Medicines Development for Global Health

CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double blind, parallel group clinical trial to evaluate the safety of moxidectin compared with ivermectin in individuals living in onchocerciasis endemic areas			
Sponsor:	Medicines Development for Global Health Level 1, 18 Kavanagh Street Southbank, Victoria 3006, Australia			
Protocol Number:	MDGH-MOX-3002			
Medical Monitor:	Dr Jolanta Airey Consultant Clinical Development Physician SJA Consulting Services, Australia Telephone: [redacted]			
Protocol Version/Date:	**Current:**	Final v02 (including Amendment 1)	**Date:**	30 Jun 2020
	Prior version:	01	**Date:**	16 Mar 2020

CONFIDENTIALITY STATEMENT

This study is being performed in compliance with Guidelines for Good Clinical Practice (GCP) as described in this protocol and all essential documents are being archived.

Until publication of this protocol following approval by the Regulatory Authority (RA) and Ethics Committees (EC) in at least one of the countries and sites conducting the study, any unpublished information contained in this document is the property of, or under the control of the Sponsor, and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and the RA and the EC. The information is only to be used by you in connection with authorized clinical studies of the investigational product described in the protocol. Prior to publication, you will not disclose any of the information to others without written authorization from the Sponsor, except to the extent necessary to obtain informed consent from those persons to whom the investigational product may be administered.

STUDY ACKNOWLEDGEMENT

A randomized, double blind, parallel group clinical trial to evaluate the safety of moxidectin compared with ivermectin in individuals living in onchocerciasis endemic areas

Protocol Number: MDGH-MOX-3002

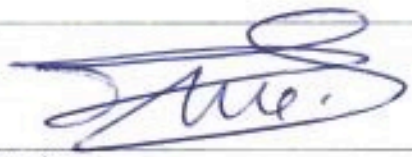
This protocol has been approved by the Sponsor. The following signature documents this approval.

MARK SULLIVAN	
Name (Printed)	Signature
	23 Oct 2020
	Date (dd mmm yyyy)

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details to conduct this study as described. I will conduct this study as outlined herein and in accordance with the principles outlined in the Declaration of Helsinki (2013), the International Ethical Guidelines for Health-related Research Involving Humans (2016), the ICH Good Clinical Practice guidelines (ICH E6(R2), 2016) and all applicable regulations and any updates to these if issued during the course of this study. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Sponsor. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

TONY UKETY	
Principal Investigator's Name (Printed)	Signature
	06 AUG 2020
	Date (dd mmm yyyy)

STUDY SYNOPSIS

Protocol No.:	MDGH-MOX-3002
Study Title:	A randomized, double blind, parallel group clinical trial to evaluate the safety of moxidectin compared with ivermectin in individuals living in onchocerciasis endemic areas.
Investigational Products:	Moxidectin, ivermectin (without or with placebo to maintain blinding)
Indication:	Onchocerciasis.
Development Phase:	3b
Treatment arms:	1. Moxidectin 8 mg per oral on Day 0; 2. Ivermectin treatment with approximately 150 microgram/kilogram (µg/kg) per oral determined based on height on Day 0. Randomization and treatment allocation will be in a ratio of 4:1
Primary objective:	To evaluate and compare the safety of a single 8 milligram (mg) dose of moxidectin with a single approximately 150 µg/kg dose of ivermectin
Primary endpoint:	Incidence and severity of treatment emergent adverse events (TEAEs)
Study design:	Randomized, double-blind, active controlled, parallel group
Number of participants:	Approximately 12,500
Study duration per participant:	Approximately 4 months.
Number of centers:	At least two
Inclusion criteria:	1. Provision of written informed consent, or assent with parental or guardian written consent. 2. Known *O. volvulus* skin microfilariae density ≥0 microfilariae/mg skin 3. Living in an onchocerciasis endemic area. 4. Age ≥ 12 years. 5. All female participants of childbearing potential must commit to the use of a reliable method of birth control until 3 months after administration of investigational product (Month 3).
Exclusion criteria:	1. Pregnant or breast-feeding. 2. Any concurrent condition that, in the opinion of the Investigator, would preclude evaluation of response to treatment or would pose undue risk to the participant's health. 3. Has received ivermectin or oral diethylcarbamazine (DEC) within 30 days of Baseline. 4. Has received treatment with an investigational agent within the 30 days (or 5 half-lives, whichever is longer) prior to planned investigational product administration. 5. Known or suspected allergy to ivermectin or moxidectin or their excipients. 6. Self-reported planned or ongoing activities within the study period that would make it unlikely that the participant will be available for follow-up examinations. 7. Infection with *Loa loa*

Study procedures:	Individuals who provide voluntary written informed consent (or for minors, assent with parental/guardian consent) will be screened for eligibility. Those meeting all of the inclusion and none of the exclusion criteria will be eligible to participate. Participants will be observed while swallowing the study treatment. Participants will be assessed for adverse events (AEs) (type, incidence, severity, seriousness, start and stop dates, and relatedness) daily for 5 days (Day 1 - Day 5). AEs reported between Day 6 and Month 3 to the study team or to health facilities in the areas where the study is conducted will be collected. Refer to the Schedule of Assessments (Table 1).
Specialized analyses:	Assessment of skin microfilariae densities for each participant will be based on two skin snips (one from each iliac crest) obtained at Screening. The samples will be weighed, immersed in normal saline for at least 8 hours and the emerging microfilariae counted by trained laboratory staff using an inverted microscope.
Sample size:	This sample size and randomization ratio will provide safety data for up to approximately 10,000 exposures to moxidectin and 2500 exposures to ivermectin, providing a probability of around 0.99 and 0.71 to detect at least one AE with a true background rate of 5/10000, respectively assuming exposures are independent.
Statistical analyses:	The participant incidence rate of TEAEs will be summarized by body system and preferred term for each treatment group and overall. Additionally, within each treatment group TEAEs will be tabulated by severity, physician assessment of relationship to investigational product, serious TEAEs and TEAEs leading to death or study withdrawal and start time. Analyses stratified by skin microfilariae densities at Screening, age and sex will be conducted. TEAEs of interest may be further analyzed via the calculation of 95% confidence intervals (CI) for participant incidence rates and/or Kaplan-Meier methods to assess time-to-first events and/or time-to-resolution. The analysis of safety endpoints will analyze participant according to the actual treatment they received.
Add-on evaluation during Screening	During Screening in selected villages in at least one study area, a ready-to-use formulation of the diethylcarbamazine (DEC) topical patch introduced by the Onchocerciasis Control Programme in West Africa for monitoring for patent *O. volvulus* infection (DEC-Patch), will be applied to the skin for a period of 24 hours. Diagnostic reaction of the skin under the DEC-Patch and attributable AEs will be recorded before administration of investigational product. The diagnostic skin reaction and DEC patch attributed AEs will be analyzed relative to the screening skin microfilariae density.
Data Safety Monitoring Board Review:	A data safety monitoring board (DSMB) will undertake regular reviews of serious adverse events (SAEs) reported during the first month after treatment, to advise the Sponsor on continued recruitment. Upon availability of exposure and safety data for children under 12 years from study MDGH-MOX-1006, a pediatric pharmacokinetic dose-finding study, and identification of a dose for children <12 years by the DSMB, the DSMB will make a recommendation on inclusion of children <12 years in this study and/or other studies. Such recommendation will trigger a protocol amendment for submission to the Regulatory Authorities and Ethics Committees for reducing the lower age limit for inclusion in this study.

Table 1: Schedule of Assessments

	Screening	Baseline		Follow Up		Early Withdrawal / Early Termination
	D-30 to D-1	D-1 to D0	D0	Daily D1 to D5 [e]	M3 End of Study (+/-1M)	
Written informed consent / assent	X					
Demography	X					
Medical History and Concurrent Conditions	X					
Prior and Concurrent Medications	X	X [d]		X	X	X
Full physical examination	X					
Height	X					
Weight	X					
Urine pregnancy test [a]	X	X [d]			X	X
***Loa loa* assessment** [b]	X					
Skin snips	X					
Determination of eligibility	X	X				
DEC-Patch application and assessment [c]	X	X				
Targeted physical examination		X [d]		X	X	X
Adverse Event Assessment	X	X	X	X	X	X
Randomization	X					
Investigational product administration			X			

Abbreviations: D: day; M: month.
[a] For women and girls of childbearing potential who will also undergo counselling on contraception.
[b] If the participant has lived or worked or still temporarily working in an area endemic for loiasis or reports symptoms compatible with *Loa loa* infection such as a history of eye worm.
[c] Some villages only. If DEC patch is applied on Day -1, the assessment of skin reactions and AEs will occur on Day 0 before investigational product administration.
[d] Targeted physical examination and concurrent medication review if > 3 days, and pregnancy test only if > 1 day, have elapsed since Screening.
[e] Participants will be visited daily by a study team member and questioned about occurrence of AEs. Medication for symptom management as required will be made available

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Table 2: Abbreviations and Acronyms

Abbreviation	Term
%	percent
<	less than
>	greater than
±	plus or minus
≤	less than or equal to
≥	greater than or equal to
°C	degrees Celsius
β-HCG	beta-human chorionic gonadotrophin
µg	microgram
µmol	micromole
AE	adverse event
APOC	African Programme for Onchocerciasis Control (1995-2015)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council of International Organizations of Medical Sciences
cm	centimeters
CNS	central nervous system
CYP	cytochrome
DAIDS	Division of AIDS
DDC	Direct Data Capture
DEC	diethylcarbamazine
DNA	Deoxyribonucleic acid
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDCTP	European & Developing Countries Clinical Trials Partnership
ELISA	Enzyme Linked Immunosorbent Assay
GABA	gamma aminobutyric acid
GCP	good clinical practice
h	hour
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
kg	Kilogram
LD_{50}	50% lethal dose
MDGH	Medicines Development for Global Health
MdSP	Ministère de la Santé publique (Ministry of Public Health) of the Democratic Republic of Congo
mf	Microfilariae
mg	Milligram
mL	Milliliter
N	Number
NDA	new drug application
NTD	neglected tropical diseases
O. volvulus	*Onchocerca volvulus*
OCP	Onchocerciasis Control Programme in West Africa
P-gp	P-glycoprotein
PICF	participant information and informed consent and assent forms
PK	pharmacokinetics
QT	cardiac Q-wave to T-wave

Abbreviation	Term
RA	regulatory authority, the governmental unit responsible for authorizing and overseeing use of investigational products
SAE	serious adverse events
SAP	statistical analysis plan
SFP	study focal point (village member(s) selected by the villagers to serve as focal point(s) within a village)
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half life
TEAE	treatment emergent adverse event
t_{max}	median time of maximum observed concentration
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WHO/TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

2 INTRODUCTION

All information applicable across all study areas is provided in the main part of this document. Information addressing requirements of regulatory authorities (RA) or ethics committees (EC) that are country specific, as well as study area specific information is provided in Attachment: Country-specific Information.

2.1 Onchocerciasis

Onchocerciasis (river blindness) is a serious, debilitating, and stigmatizing parasitic disease caused by the helminth *Onchocerca volvulus* (*O. volvulus*). It is recognized as an important public health issue by health authorities worldwide and is listed by the World Health Organization (WHO) (African Programme for Onchocerciasis Control 2015) and United States (US) Food and Drug Administration (FDA) (The Henry J. Kaiser Family Foundation 2015) as one of the Neglected Tropical Diseases (NTDs) for which new treatments are sought.

Onchocerciasis is endemic in sub-Saharan Africa. More than 200 million people are currently considered to be at risk of infection (World Health Organization 2018). Onchocerciasis is the second leading cause of infectious blindness (after trachoma) and the fourth leading cause of preventable blindness worldwide. In addition to substantial ocular and cutaneous morbidity, excess mortality of visually impaired and non-impaired individuals with heavy onchocercal infection accounted for 5% of deaths in the area of the Onchocerciasis Control Program in West Africa (a WHO managed international collaboration that ran between 1974 to 2002) (Prost and Vaugelade 1981, Pion et al. 2002, Little et al. 2004).

O. volvulus larvae are transmitted to humans by the bite of black flies (genus *Simulium*), which breed in fast-flowing rivers and streams. The larvae develop into mature adult worms (macrofilariae) and become encapsulated in nodules, from which they release millions of microfilariae that migrate through the skin and into the eyes. Macrofilariae have an estimated life span of approximately 10 to 14 years. The *O. volvulus* microfilariae are the cause of the clinical manifestations of onchocerciasis which include pruritus, dermatitis, depigmentation and atrophy of the skin, lymphadenitis, and visual impairment leading to blindness. The skin microfilariae are the reservoir of transmission of the parasite by the vector (Remme et al. 2017)

The Global Burden of Disease 2013 study estimated that onchocerciasis is the sixth highest cause of NTD-related years lived with disability, predominantly due to onchocercal skin disease (Herricks et al. 2017). In the Global Burden of Disease study 2017, it was identified as the leading cause of years lived with disability for the Democratic Republic of the Congo (DRC) (Vos et al. 2017). The disease reduces income-generating capacity, incurs substantial health expenditures, and exerts a devastating socioeconomic effect on already challenged communities.

2.2 Current Treatment and Unmet Need

Ivermectin is an endectocide approved in 1996 for the treatment of onchocerciasis in the US and is available through the Mectizan Donation Program to all onchocerciasis endemic countries, including 29 countries in sub-Saharan Africa, for treatment of onchocerciasis. It is the current standard of care for onchocerciasis. The recommended regimen for the treatment of onchocerciasis is a single oral dose of ivermectin 150 µg/kg.

In sub-Saharan Africa, including the DRC, ivermectin mass drug administration is now the standard strategy of onchocerciasis control programs. It is implemented as community

directed treatment with ivermectin, with height, rather than weight-based dosing, and most commonly with a retreatment interval of 12 months. More than 200 million people are currently considered to require community directed treatment with ivermectin. In the DRC, 39.8 million people received ivermectin in 2018 among an estimated 50.4 million requiring mass drug administration (World Health Organization 2018).

Epidemiological evaluations via microscopic examination of skin snips and health impact assessments conducted by the African Programme for Onchocerciasis Control (APOC, 1995 to 2015) in collaboration with country control programs (including in the DRC) have shown that long term community directed treatment with ivermectin significantly reduces *O. volvulus* infection prevalence and morbidity (Coffeng et al. 2014, Tekle et al. 2016).

Despite the positive impact of ivermectin treatment, onchocerciasis is still a cause of significant morbidity. Incomplete clearance of dermal or ocular microfilariae and/or rapid repopulation have been observed in a substantial subset of both ivermectin-naïve and ivermectin-experienced *O. volvulus*-infected individuals (African Programme for Onchocerciasis Control , Awadzi et al. 2004, Awadzi et al. 2004, Ardelli et al. 2005, Osei-Atweneboana et al. 2007, Basanez et al. 2008, Pion et al. 2011, Bakajika et al. 2013, Coffeng et al. 2013). This also occurred in ivermectin-treated participants in the moxidectin Phase III study, which included 472 participants from Ituri and 487 from Nord-Kivu of the DRC (Opoku et al. 2018). Using a responder definition of < 20% of pre-treatment skin microfilariae density at 6 months and ≤ 40% of pre-treatment skin microfilariae density at 12 months, there were no suboptimal responders at Month 6 in the moxidectin group and 10/941 (1.1%) at Month 12. By contrast, 59/492 (12.0%) and 88/481 (18.3%) ivermectin recipients were suboptimal responders at Months 6 and 12, respectively.

The primary goal of onchocerciasis control in Africa has recently shifted from control as a public health problem (reduction of morbidity and transmission in meso- and hyperendemic areas: i.e. areas with villages with around 35 to 60% and > 60% infection prevalence, respectively (Prost 1987)) to elimination of infection and transmission across all endemic areas. The time of elimination using ivermectin alone is predicted to be after 2040 in some territories (Kim et al. 2015). As summarized by APOC, which supported onchocerciasis control until 2015, the global health community recognizes that onchocerciasis will not be eliminated without new tools and strategies (African Programme for Onchocerciasis Control 2015).

In the Phase II and III studies conducted in Ghana, Liberia and the DRC (Ituri, Nord Kivu), a single dose of moxidectin was superior to a single dose of ivermectin in reducing microfilaridermia and in maintaining low microfilariae densities for 18 months after dosing (Awadzi et al. 2014, Opoku et al. 2018). Consequently, moxidectin has the potential to accelerate progress towards elimination of onchocerciasis (Turner et al. 2015).

2.3 Moxidectin

Moxidectin is a macrocyclic lactone of the milbemycin class. It is semi-synthetically derived from the actinomycete *Streptomyces cyanogriseus*.

Evaluation of moxidectin for its utility for onchocerciasis control was initiated by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) executed by WHO. The pharmaceutical company with which WHO/TDR was working for potential regulatory registration of moxidectin discontinued the collaboration. WHO licensed all data to Medicines Development for Global Health (MDGH), the Sponsor of this study. MDGH raised the funds, initiated discussions for registration with the US FDA, completed development and assembly of the New Drug

Application (NDA) and submitted the NDA to the US FDA in 2017 (Sullivan and Kuesel 2018).

Moxidectin 8 mg was approved in June 2018 by the US FDA for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older (information available at www.accessdata.fda.gov/scripts/cder/daf).

This current study is a large single-dose safety study, based on discussions with the WHO and is part of a study program sponsored by MDGH. Two additional studies are being conducted in Africa within this program. Those studies address commitments MDGH made to the US FDA and include: a study of the safety and efficacy of annual or biannual doses of moxidectin or ivermectin for treatment of onchocerciasis in people 12 years and older (MDGH-MOX-3001, Study 3001) and a pediatric study to determine the moxidectin dose in 4 to 11 year olds (MDGH-MOX-1006, Study 1006, in preparation). Both are therefore being conducted under a US FDA Investigational New Drug (IND) Application. For further information see Sections 15.23 and 18.

This section presents a brief summary of the known preclinical and clinical data of moxidectin that formed the basis for the June 2018 US FDA approval. A detailed description of the chemistry, pharmacology, efficacy and safety of moxidectin is provided in the current moxidectin Investigator's Brochure. The current approved prescribing information for use of moxidectin tablets for onchocerciasis is available at Drugs@FDA (www.fda.gov/drugsatfda).

2.3.1 Non-clinical Data

2.3.1.1 Pharmacology

The primary pharmacology of moxidectin is proposed to be through binding to the glutamate-gated chloride channels. Moxidectin also binds to gamma-aminobutyric acid (GABA) receptors and/or adenosine triphosphate-binding cassette transporters. This leads to increased permeability, influx of chloride ions, hyperpolarization and muscle paralysis (Arena et al. 1995, Martin et al. 2002, Yates et al. 2003). Additionally, there is a reduction in parasite motility (Tompkins et al. 2010) and reduced excretion of immunomodulatory proteins of both male and female adult worms (Wolstenholme and Rogers 2005, Geary and Moreno 2012, Wolstenholme et al. 2016). Studies also suggest that while moxidectin is not effective in killing adult worms, it does reduce adult worm fertility (Bourguinat et al. 2007, Stitt et al. 2011).

Moxidectin exhibits anthelminthic activity across the nematode and arthropod phyla (Geary and Moreno 2012) and has demonstrated efficacy in a number of *Onchocerca* species, including *O. ochengi* in cattle (Trees et al. 2000), *O. cervicalis* in horses (Monahan et al. 1995, Mancebo et al. 1997), as well as *Dirofilaria immitis* in dogs (Nolan and Lok 2012). Moxidectin was not macrofilaricidal in the *O. ochengi* model in cattle (Trees et al. 2000).

For further information, please refer to the Investigator's Brochure.

2.3.1.2 Non-clinical Safety

2.3.1.2.1 Safety Pharmacology

The safety pharmacology of moxidectin has been studied using a panel of *in vitro* and *in vivo* pulmonary, neurofunctional and cardiac assessments. Moxidectin did not show significant binding activity to 64 different biological receptors in the NovaScreen assay. The IC_{50} value for a 50% decrease in the human Ether-a-go-go Related Gene current was calculated at > 10 micromolar (µM) (6.4 µg/milliliter (mL)) moxidectin.

Moxidectin caused mild neurofunctional and respiratory effects in rats as well as a mild reduction in heart rate relative to baseline in dogs. Oral administration of 1.0 mg/kg moxidectin to beagle dogs resulted in a statistically significant decrease in heart rate, but no consistent changes in systolic, diastolic or mean arterial blood pressure. There were no effects on the electrocardiogram (ECG), including the cardiac Q-wave to T-wave (QT) interval.

For more information, please refer to the Investigator's Brochure.

2.3.1.2.2 Toxicology

The nonclinical toxicology profile of moxidectin is characterized by low acute toxicity, consisting mostly of transient central nervous system (CNS)-related clinical signs. Decreased body weight and/or body weight gain were also common findings, which were attributed to a change in consumption of food. In single and repeat dose toxicity studies with moxidectin, transient CNS signs were reported in mice, rats and dogs. There was no target organ toxicity in any of the studies based on evaluation by clinical and anatomic pathology.

Moxidectin was not genotoxic and showed no carcinogenic potential in lifetime mouse and rat bioassays. Moxidectin resulted in increased incidence of malformations in rats at maternally toxic doses, but not in rabbits, and decreased pup survival during the lactation period in one and three generation pre- and post-natal rat studies.

Macrocyclic lactones are known to interact with GABA-A receptors, expressed in nematodes and in the mammalian CNS. There was no histological evidence for direct neurotoxicity of moxidectin in nonclinical studies, but transient neurobehavioral effects were noted. Entrance into the brain is restricted by the P-glycoprotein (P-gp) efflux transporter, while toxicity is mediated through the brain GABA-A receptors. In P-gp-deficient mice, moxidectin was less toxic than ivermectin (50% lethal dose (LD_{50}) was 0.46 and 2.3 micromole (µmol)/kg for ivermectin and moxidectin, respectively), had a lower brain-to-plasma concentration ratio and entered into the brain more slowly than ivermectin (Menez et al. 2012). Higher brain concentrations are required for moxidectin toxicity than ivermectin, which causes a greater potentiation of GABA action. Differences in the accumulation of ivermectin and moxidectin in the brain and in the interaction of ivermectin and moxidectin with GABA-A receptors account for differences in neurotoxicity seen in nonclinical studies (Menez et al. 2012).

For more information, please refer to the Investigator's Brochure.

2.3.1.3 Absorption, Distribution, Metabolism and Excretion

Moxidectin is a Biopharmaceutics Classification System Class 2 compound with high permeability and low solubility, which is not affected by pH.

The pharmacokinetics of moxidectin in rats and dogs was characterized by oral absorption, low plasma clearance, and a high volume of distribution, leading to a long terminal elimination half-life ($t_{½}$). The distribution of moxidectin is governed primarily by its high degree of lipophilicity; in rats, moxidectin was shown to be distributed to and reside predominantly in fat. Moxidectin is minimally metabolized *in vivo*. Moxidectin has also been shown to be a weak substrate of breast cancer resistance protein/ABCG2 (Perez et al. 2009). Moxidectin produced weak or no inhibition of seven major human cytochrome (CYP) P450 enzymes *in vitro* but did induce CYP3A4 messenger ribonucleic acid and enzyme activity *in vitro*. However, a subsequent clinical study showed that moxidectin was not a CYP3A4 inducer *in vivo* (Section 2.3.2.1).

In rats, moxidectin is likely cleared by a combination of biliary excretion of unchanged drug and oxidative metabolism.

For more information, please refer to the Investigator's Brochure.

2.3.2 Clinical Data

The moxidectin clinical program to date encompasses eight single oral dose trials spanning Phases I to III and involving a total of 1904 participants.

In the six Phase I studies, 243 healthy volunteers received moxidectin at doses of 3 to 36 mg and 16 healthy volunteers received placebo:

- A single-ascending dose, placebo-controlled, double-masked, safety, tolerability, and pharmacokinetic study of orally administered moxidectin in normal volunteers (Study 100, protocol 3110A1-100-EU) (Cotreau et al. 2003);
- A study of the relative bioavailability of a tablet and a liquid formulation of moxidectin in healthy participants (Study 101, protocol 3110A1-101-EU) (Korth-Bradley et al. 2012);
- An open-label, single-dose study to evaluate the excretion of moxidectin into the breast milk of lactating, non-breastfeeding women (Study 1002, protocol 3110A1-1002-EU) (Korth-Bradley et al. 2011);
- An open-label, single-dose, four-period, sequential study to determine the effect of moxidectin on CYP3A4 activity in healthy participants using midazolam as a probe substrate (Study 1004, protocol 3110A1-1004-EU) (Korth-Bradley et al. 2014);
- An open-label, randomized, single-dose, parallel-group study to determine the effect of a high-fat meal on the relative bioavailability and pharmacokinetics of a single dose of moxidectin administered orally to healthy participants (Study 1005, protocol 3110A1-1005-EU) (Korth-Bradley et al. 2012); and
- A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the potential effect of a single oral dose of moxidectin on the cardiac Q-wave to T-wave (QT interval) of healthy volunteers (Study 1008, protocol MDGH-MOX-1008) (Kinrade et al. 2018).

In one Phase II and one Phase III study enrolling participants with onchocerciasis, 1105 participants received moxidectin at doses of between 2 and 8 mg while 539 received ivermectin at the standard-of-care dose of 150 microgram (µg)/kg and as used in ivermectin-based control programs:

- A randomized, single-ascending-dose, ivermectin-controlled, double-blind, safety, tolerability, pharmacokinetic, and efficacy study of orally administered moxidectin in participants with *Onchocerca volvulus* infection (Phase II, protocol 3110A1-200-GH) (Awadzi et al. 2014); and
- A single dose, ivermectin-controlled, double blind, efficacy, safety, and tolerability study of orally administered moxidectin in participants infected with *Onchocerca volvulus* (Phase III, protocol ONCBL60801) (Opoku et al. 2018).

2.3.2.1 Clinical Pharmacology

Moxidectin displays linear, dose-proportional pharmacokinetics. Following a single oral moxidectin dose administered to fasting healthy volunteers, the non-compartmentally-derived apparent moxidectin plasma clearance ranged from 2760 to 3506 mL/hour in healthy volunteers and was 3500 mL/hour in *O. volvulus* infected individuals. The mean $t_{½}$ ranged from 485 to 1139 hours (approximately 20 to 47 days) in healthy volunteers and was 559

hours in *O. volvulus* infected individuals. Moxidectin was rapidly absorbed; the median time of maximum observed plasma concentration (t_{max}) in a fasted state was 3 to 4 hours post-dose. Moxidectin has a large apparent volume of distribution, and rapid decline of moxidectin concentrations occurred within 48 hours of dose administration in all studies, and, thereafter, plasma concentrations declined slowly in accordance with the long $t_{½}$. Population pharmacokinetic analyses showed that the long $t_{½}$ was governed by tissue distribution rate-limited elimination.

There were no clinically relevant effects of age, sex, race, weight, renal function or hepatic function on the pharmacokinetics of moxidectin from a population-pharmacokinetic model. Moxidectin absorption is resilient to the effects of food. Administration of moxidectin in a fed state modestly slows absorption and increases bioavailability, although not to a clinically relevant extent. Moxidectin does not induce or inhibit clinically relevant drug-drug interactions and it is unlikely to be a victim of drug-drug interactions via concomitant medications.

Moxidectin is minimally metabolized and primarily excreted unchanged in the feces. Renal clearance of moxidectin and its metabolites is low. Moxidectin was observed in the breast milk of lactating women after single dose administration at a relative infant dose of less than 10% of the maternal dose.

For more information, please refer to the Investigator's Brochure.

2.3.2.2 Clinical Safety

2.3.2.2.1 Overview of Safety in Healthy Volunteers

Safety data are available from 6 studies in healthy adult volunteers. Moxidectin was well tolerated when given as a single dose of between 3 and 36 mg to healthy volunteers. There was no treatment or dose relationship in the incidence, nature and severity of AEs identified. There were no clinically relevant or treatment-related changes in laboratory parameters, physical examination findings, vital signs or electrocardiograms (ECGs)/cardiac function. In placebo-controlled studies, moxidectin had a safety profile similar to placebo. No participant withdrew due to an AE and there were no SAEs or deaths.

AE and laboratory findings reported for each of the completed Phase I studies are summarized in the Investigator's Brochure.

2.3.2.2.2 Overview of Safety in Individuals with Onchocerciasis

In individuals infected with *O. volvulus* who received treatment that led to the death of microfilariae, the common AEs observed are the signs and symptoms associated with microfilariae death, i.e. drug efficacy associated AEs, referred to as the "Mazzotti reaction". These reactions are caused by an immune reaction to the dead and dying microfilariae and manifest as pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia. Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision, photophobia, changes in visual acuity, hyperemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment.

The safety of moxidectin has been evaluated in comparison to the safety of ivermectin in two studies in *O. volvulus* infected individuals (3110A1-200-GH and ONCBL60801) (Awadzi et al. 2014, Opoku et al. 2018). In both studies, the profile of AEs reported for individuals having received moxidectin was similar to the profile in ivermectin recipients.

In these studies, the most commonly occurring events were signs and symptoms attributable to the body's response to dying microfilariae: pruritus, edema, headache, hypotension and compensatory tachycardia, rash and urticaria, myalgia, arthralgia, pyrexia and chills, lymphadenopathy, paresthesia and asthenia. These events were transient and self-limiting, generally occurring and resolving within the first week of treatment. In general, there was a transient (first 48 hours) increase in the number of moxidectin participants reporting efficacy-associated AEs compared to ivermectin. There was not an increased need for medical or therapeutic intervention for management of efficacy-related events with moxidectin when compared to ivermectin. Given that the spectrum of symptoms and severity were similar, the treatment guidance to patients and physicians in the US FDA prescribing information for moxidectin are otherwise unchanged compared to ivermectin.

Treatment Emergent Adverse Events (TEAEs) occurring in > 10% of moxidectin-treated participants in the Phase III study compared with ivermectin-treated participants are summarized in Table 3.

For further information refer to the Investigator's Brochure.

Table 3: Treatment Emergent Adverse Events Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in ONCBL60801 (Phase III)

Treatment Emergent Adverse Events	Moxidectin N = 978 n (%)	Ivermectin N = 494 n (%)
Eosinophilia	721 (74)	390 (79)
Pruritus	640 (65)	268 (54)
Musculoskeletal pain [a]	623 (64)	257 (52)
Headache	566 (58)	267 (54)
Lymphocytopenia*	470 (48)	215 (44)
Tachycardia [b]	382 (39)	148(30)
Orthostatic tachycardia [c]	333 (34)	130 (26)
Non-orthostatic tachycardia [d]	179 (18)	57 (12)
Rash [e]	358 (37)	103 (21)
Abdominal pain [f]	305 (31)	173 (35)
Hypotension [g]	289 (30)	125 (25)
Orthostatic hypotension [h]	212 (22)	81 (16)
Pyrexia/Chills	268 (27)	88 (18)
Leukocytosis	240 (25)	125 (25)
Influenza like illness	226 (23)	102 (21)
Neutropenia**	197 (20)	112 (23)
Cough	168 (17)	88 (18)
Lymph node pain	129 (13)	28 (6)
Dizziness	121 (12)	44 (9)
Diarrhea/Gastroenteritis/Enteritis	144 (15)	84 (17)
Hyponatremia	112 (12)	65 (13)
Peripheral swelling	107 (11)	30 (6)

[a] Includes "myalgia", "arthralgia", "musculoskeletal pain", "pain" and "back pain"
[b] Includes "orthostatic heart rate increased", "postural orthostatic tachycardia syndrome", "heart rate increased" and "sinus tachycardia"
[c] Includes "orthostatic heart rate increased" and "postural orthostatic tachycardia syndrome"
[d] Includes "heart rate increased", "tachycardia", and "sinus tachycardia"
[e] Includes "rash," "papular rash" and "urticaria"
[f] Includes "abdominal pain", "abdominal pain upper" and "abdominal pain lower"
[g] Includes "orthostatic hypotension", "blood pressure orthostatic decreased", "blood pressure decreased", "mean arterial pressure decreased", "hypotension"
[h] Includes "orthostatic hypotension", and "blood pressure orthostatic decreased"
*Lymphocytopenia is defined as absolute lymphocyte count less than 1 x 10^9/L
**Neutropenia is defined as absolute neutrophil count less than 1 x 10^9/L

There was no pattern indicating a temporal association with treatment or with body system of SAEs occurring in either the 3110A1-200-GH or the ONCBL60801 studies. In both

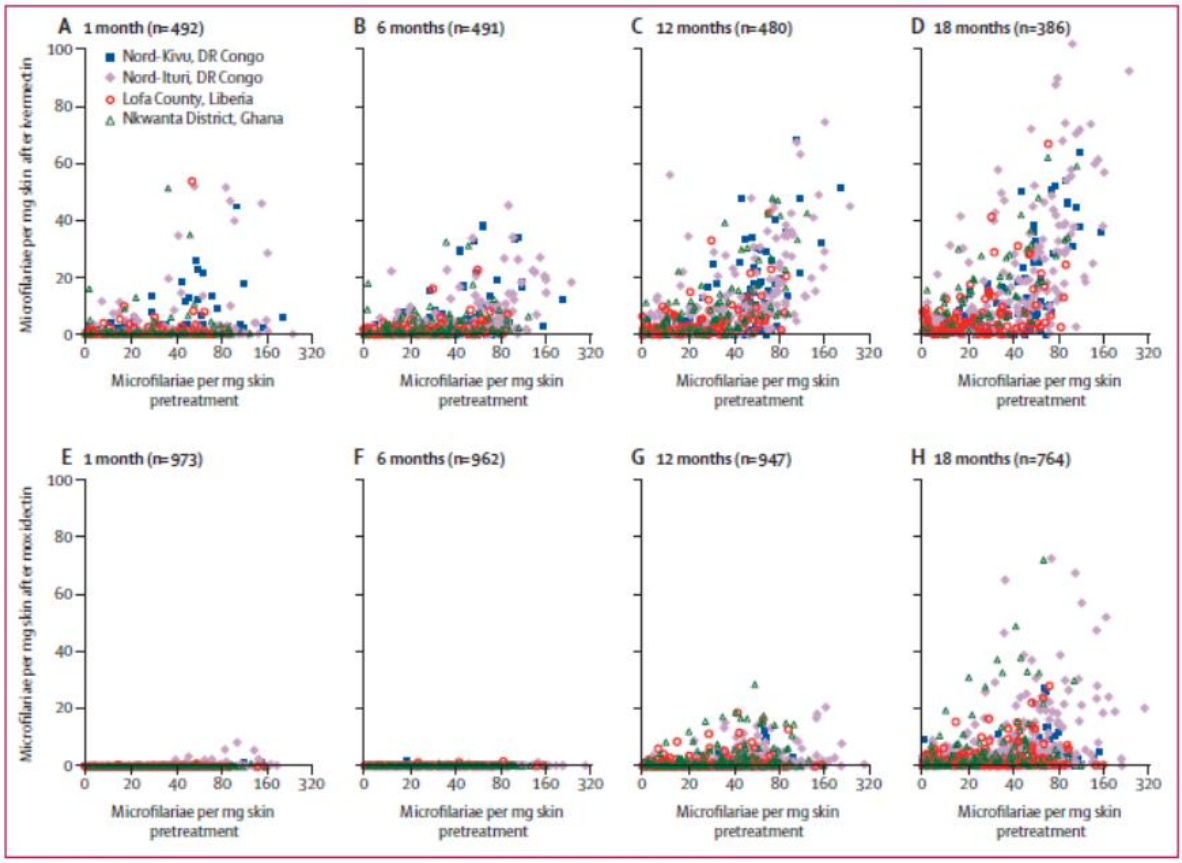
studies, there were no SAEs regarded by the investigator (or Sponsor) as being treatment-related. Treatment-emergent SAEs (occurring during the first 180 days post-dose) are presented in the Investigator's Brochure.

2.3.2.3 Clinical Efficacy

In the two studies conducted in *O. volvulus* infected individuals (3110A1-200-GH and ONCBL60801), a single dose of moxidectin was superior to a single dose of ivermectin in reducing skin microfilariae density and maintaining low skin microfilariae density (Awadzi et al. 2014, Opoku et al. 2018).

In the Phase III study (ONCBL60801), the mean skin microfilariae density at 12 months after treatment was significantly lower in the moxidectin group (1.79 mf/mg) than in the ivermectin group (9.83 mf/mg) (95% Confidence Interval (CI) for the difference -9.11, -6.98, $p < 0.0001$) (moxidectin Prescribing Information, available at www.fda.gov/drugsatfda). Skin microfilariae densities were also significantly lower in the moxidectin than the ivermectin treatment group at all other post-treatment time points evaluated in this study Figure 1).

Figure 1: Skin Microfilariae Densities 1, 6, 12 And 18 Months after a Single Dose of Ivermectin (A-D) and after a Single Dose of Moxidectin (E-H) in the Phase III Study By Study Area and Pre-Treatment Skin Microfilariae Density



X-axis shows pre-treatment skin microfilariae density on a logarithmic scale; y-axis shows post-treatment skin microfilariae density on an arithmetic scale. From Opoku, Bakaj ka et al. 2018 (Opoku et al. 2018).

Both ivermectin and moxidectin reduced the number of live microfilariae in the anterior chambers of the eyes.

2.4 Study Overview

Onchocerciasis is endemic primarily in rural areas of sub-Saharan Africa. Given the health system capacities in these areas in conjunction with the fact that there is no large-scale suitable diagnostic for pre-patent or patent infection with *O. volvulus*, the strategy for onchocerciasis control and elimination is now based on mass drug administration. Mass drug administration requires that the safety profile of a drug is established in uninfected individuals, as well as infected individuals requiring treatment.

As summarized above and in the Investigator's Brochure, the profile of AEs reported in the Phase II and III studies among the 1016 *O. volvulus* infected individuals treated with 8 mg moxidectin was similar to the profile among the 539 *O. volvulus* infected individuals treated with the dose of ivermectin used during ivermectin mass drug administration (approximately 150 µg/kg). The safety data from the 228 healthy volunteers who received between 8 mg and 36 mg moxidectin showed that moxidectin is well tolerated in individuals not infected with *O. volvulus*.

This study is designed to significantly increase the safety database occurring in *O. volvulus* infected as well as uninfected individuals after treatment with a single dose of 8 mg moxidectin compared to ivermectin. It is being conducted based on discussions with the WHO Neglected Tropical Disease department to provide WHO and Ministries of Health of onchocerciasis endemic countries with more safety data to inform their decisions on whether to include mass moxidectin administration in guidelines and policies for onchocerciasis control and elimination programs.

Two additional studies are being conducted to further support these decisions and address commitments MDGH made to the US FDA:

(a) A study to compare the safety and efficacy of three annual and five biannual treatments with moxidectin or ivermectin of *O. volvulus* infected people 12 years and older (MDGH-MOX-3001, Study 3001). Study 3001 is being conducted to provide WHO and Ministries of Health of endemic countries with a better estimate of the relative benefit of moxidectin vs. ivermectin based annual and biannual mass drug administration strategies for progress towards onchocerciasis elimination than modelling can provide (Turner et al. 2015)

(b) A pediatric pharmacokinetic and safety study to determine a moxidectin dose for 8 to 11 year olds and 4 to 7 year olds (MDGH-MOX-1006, Study 1006).

2.4.1 Design Rationale

This study is a randomized, double blind, active controlled parallel group study to minimize bias in treatment allocation and AE reporting by participants and AE recording and assessment by study staff.

Randomization to moxidectin and ivermectin in a ratio of 4:1 has been chosen to maximize data on AEs after moxidectin treatment while providing a concurrent ivermectin control.

Randomization will be stratified by screening skin microfilariae density (<20 mf/mg skin vs. ≥20 mf/mg skin) because the frequency and severity of some Mazzotti reactions depend significantly on pre-treatment skin microfilariae density (Opoku et al. 2018).

Each site will be provided with its own set of randomization lists which will minimize confounding effects of concurrent locally occurring adverse events unrelated to investigational product administration (see Section 8.1, Section 14.3).

2.4.2 Study Population and Locations

The study population is planned to be as representative of the population participating in mass drug administration as possible based on currently available safety data. Consequently, inclusion of both *O. volvulus* infected and uninfected individuals and both ivermectin-naïve and ivermectin-experienced individuals is allowed. Individuals will be ineligible only if they meet criteria inconsistent with current US FDA approved labelling for moxidectin, with one exception: individuals without evidence of *O. volvulus* infection as determined by microscopic examination of skin snips are eligible. Exclusion criteria include pregnancy, breast-feeding, unwillingness to commit to contraception; infection with *Loa loa*; concurrent conditions that per the investigator's judgement would result in undue health risk or jeopardize evaluation of the response to ivermectin or moxidectin; or reported ongoing or planned activities that would make participation in the planned follow up examinations unlikely. For further details of the rationale for the eligibility criteria, see Sections 6.3 and 6.4. Moxidectin prescribing information is available at www.accessdata.fda.gov/scripts/cder/daf) and ivermectin prescribing information at https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf , http://edenbridgepharma.com/Ivermectin%20PI.pdf).

The study is planned to be conducted in at least two different areas within Africa, ideally two different countries. Study area/country specific information is provided in Attachment: Country-specific Information.

2.4.3 Evaluation during Screening of a Tool for Identifying Patent *O. volvulus* infection

As countries move towards onchocerciasis elimination, tools are needed to determine the residual prevalence of infection and to monitor potential re-emergence of transmission following cessation of mass drug administration.

The only currently available method for identifying current (patent) infection is based on taking pieces of skin (skin snips) and investigating them, via microscopy or polymerase chain reaction, for presence of *O. volvulus* parasites or deoxyribonucleic acid (DNA), respectively. Skin snipping with microscopic examination is the standard method for drug efficacy research. It has also been used by APOC and onchocerciasis endemic countries to determine residual infection prevalence in areas having undergone long term mass ivermectin distribution in Burundi, the Central African Republic, Chad, the Republic of Congo, the Democratic Republic of the Congo, Ethiopia, Liberia, Malawi, Nigeria, Tanzania, and Uganda (Tekle et al. 2016). However, skin snipping is a laborious, time consuming method, suitable for research but not for large scale use by onchocerciasis elimination programs.

Detection of antibodies to the *O. volvulus* antigen OV16 via Enzyme Linked Immunosorbent Assay (ELISA), recommended in the current WHO guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis (World Health Organization 2016), cannot distinguish between patent and past infection. Discussions continue on the accuracy of different ELISA and the currently available Rapid Diagnostic Test.

The Onchocerciasis Control Programme in West Africa (OCP) introduced a patch prepared *ad hoc* from diethylcarbamazine (DEC) in a skin lotion (OCP-patch) as a non-invasive and specific diagnostic test for monitoring patent *O. volvulus* infection (Toe et al. 2000, Organisation mondiale de la Santé and Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest 2002, World Health Organization and Onchocerciasis Control

Programme in West Africa 2002). The disadvantage of the OCP-patch is the *ad hoc* preparation (DEC dispersion in lotion, that is then applied to a piece of filter paper, which is attached with adhesive plaster to the skin), a labor intensive procedure for large scale use (Organisation mondiale de la Santé and Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest 2002, World Health Organization and Onchocerciasis Control Programme in West Africa 2002). Furthermore, neither DEC concentration nor homogeneity in the lotion nor a standardized lotion amount on the filter paper can be assured.

At the request of OCP and APOC, WHO/TDR managed development of a ready-to-use patch with standardized DEC content (DEC-Patch) manufactured according to current Good Manufacturing Practices. A clinical study in 30 *O. volvulus* infected individuals which showed similar sensitivity and a better safety profile of the DEC-Patch compared to the OCP-Patch (Diawara et al. 2009, Awadzi et al. 2015). In a large epidemiological field study, the DEC patch was applied to 2283 individuals. While not all returned for the 24 hour reading, no skin reactions was identified among those who did (number not specified), consistent with no microfilariae having been detected in skin snips and suggesting that the DEC-patch has high specificity (Diawara et al. 2009, Awadzi et al. 2015). Following the recommendation of the Technical Consultative Committee of APOC, WHO entered into a legal agreement with the manufacturer (Lohmann Therapie Systeme, Andernach, Germany) to manufacture the DEC-Patch for WHO. Lohmann Therapie Systeme provides the DEC patch to WHO at cost but does not make it commercially available.

The APOC Technical Consultative Committee also recommended large scale evaluation of the patch in different areas with different levels of endemicity (Awadzi et al. 2015).

The large number of individuals screened in this study provides an excellent opportunity to implement this recommendation. Consequently, it is planned to administer the DEC-Patch during screening of individuals for this study in selected villages. The DEC-Patch will be removed and data on adverse events and the diagnostic skin reaction under the patch area collected before investigational product is administered to individuals found to be eligible for the study.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate and compare the safety of a single 8 milligram (mg) dose of moxidectin with a single dose of approximatively 150 µg/kg of ivermectin.

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint for this study is the participant incidence rate of TEAEs.

3.3 Evaluation of the DEC-Patch during Screening

The objectives of the add-on evaluation are to assess the

- safety of the DEC-Patch; and
- diagnostic skin reaction under the DEC-Patch relative to the presence of skin microfilariae determined by skin snip.

This will be based on the following endpoints:

- The participant incidence rate of adverse events attributable to the DEC-Patch (assessed prior to administration of moxidectin or ivermectin)

The intensity of the diagnostic skin reaction under the DEC-Patch.

4 STUDY DESIGN

4.1 Study Design

This is a randomized, double blind, active controlled, multi center, parallel group clinical trial.

4.2 Dosing Regimens

Participants will be randomized to one of the following two treatment regimens:

1. Single dose moxidectin: 8 mg per oral given on Day 0.
2. Single dose ivermectin: approximately 150 µg/kg per oral given on Day 0.

To maintain the study blind, all participants will receive four capsules (Section 8.6).

4.3 Number of Participants and Randomization

Approximately 12,500 eligible participants will be randomized in a ratio of 4:1 to moxidectin or ivermectin treatment, respectively. Ideally each recruitment area will randomize similar numbers of participants. Pre-established randomization quotas or caps per recruitment area are not planned.

4.4 Study Sites

See Section 5.5; Attachment: Country-specific Information.

4.5 Study Duration for Each Participant

The study duration for each participant is approximately 4 months, including approximately 1 months for Screening and 3 months for follow up.

4.6 Estimated Duration of the Study

It is anticipated that the total duration of the study from initiation to completion will be approximately 19 months, comprised of approximately 12 months for recruitment, 4 months screening, treatment and post-treatment follow up, and 3 months for data analysis and reporting.

5 PRE-STUDY ENGAGEMENT

5.1 Community Mobilization

All relevant Communities will be provided with general information about onchocerciasis and its control, clinical research, and the moxidectin study(ies) planned to be conducted in the area.

For the purpose of this study, "Community" includes the following groups:

- Government authorities and members of the regional/provincial and national parliament representing the area from which participants will be recruited;
- Civil society (e.g. associations of different professional, religious groups, non-governmental organizations);
- Health care authorities, including the onchocerciasis and, if applicable, lymphatic filariasis control and elimination programs;
- Maternal and Child Health/Reproductive Health/Family Planning programs (as applicable)
- Staff of the local health care facilities;
- Local staff of non-governmental organizations supporting health care and onchocerciasis and, if applicable, lymphatic filariasis programs;
- Staff of local news, radio stations and social media (local media);
- Village/community leaders and elders, religious leaders; and
- Inhabitants of all villages in the trial areas from which study participants are planned to be recruited (Section 5.5; Attachment: Country-specific Information).

5.2 Coordination and Collaborations with the Local Health System

5.2.1 National Program for Neglected Tropical Diseases (Onchocerciasis and Lymphatic Filariasis Control/Elimination)

Conduct of this study will be in consultation with the national program for control and elimination of onchocerciasis (and lymphatic filariasis where study areas are co-endemic).

5.2.2 Maternal Health/Reproductive Health/Family Planning Program (as applicable)

This study will be conducted in consultation with the local health system programs for maternal health/ reproductive health/Family Planning (as applicable) so that the contraceptives offered to study participants are consistent with those offered by these programs. This will also ensure that study messaging on contraception will be consistent with the messaging of these programs.

5.2.3 Local Health Facilities

A collaborative relationship will be established with all local healthcare facilities that study participants might approach for AEs (whether study-related or not). This is to ensure that the study team will be informed about and can report the relevant data in the electronic Case Report Form (eCRF) for the following:

(1) AEs reported by study participants along with any medication/procedures provided by the local healthcare staff;

(2) the findings during ante-natal care visits and any medication/procedures provided by the local health care staff should a study participant become pregnant within 3 months after investigational product administration (or the partner of a study

participant becoming pregnant during the equivalent time period, provided she agrees to the study team accessing these data);

(3) the findings of post-natal care visits during the first year of life of any babies born to study participants becoming pregnant within 3 months after investigational product administration (or the partner of a study participant becoming pregnant during the equivalent time period, provided she agrees to the study team accessing these data).

Study participants will be informed about the need for collection of these data from the local health facilities and consent (or assent with parental/guardian consent) to this (see Section 6.1 and 15.9). All data collected from local health facility records during the study are subject to the same confidentiality provisions as data collected directly by the study team (see Section 15.17 and Section 17).

Staff of these facilities will receive training on this study, with particular emphasis on AEs expected after treatment with ivermectin or moxidectin (see Section 10.5), assessment of AEs and current Good Clinical Practice (GCP) compliant documentation.

5.2.4 Village Members Involved in Implementation of Public Health Measures

Collaboration will be established with villagers who are involved in implementation of public health measures in their village, including, but not limited to Community-Directed Distributors of Ivermectin for onchocerciasis control and elimination.

Collaboration with them will be sought when they are selected by the village communities as points of contact (Study Focal Point, SFP) with the study team within their villages. The SFP will also be part of the system established for facilitating participants contacting the study team or local health centers when they experience AEs outside the scheduled study team visits and for reminding participants of upcoming follow up visits by the study team. They will furthermore be the conduit for any complaints the study participants have regarding the study conduct for those participants who prefer not to convey these complaints directly or via another person of their choice (such as the village chief).

It is anticipated that depending on the size of a village and the geographic terrain it covers the number of villagers already involved in facilitating implementation of public health measures in their villages (and/or those willing and selected by the village community to be an SFP) may be below the number of SFP necessary. Depending on the outcome of discussions with the village leaders and elders and during community meetings, villagers will be asked to select additional community members as SFP for this study during the initial meetings and consultation (Section 5.5).

The SFP will receive the training on this study they require to fulfill their role in this study, be provided with the material they need (for example a mobile phone with phone units) and compensated for the time they spend on study related activities.

5.3 Information to Local Media

Information to staff of local media (local online or print news, radio, and/or social media) will be provided to ensure that they have correct information about clinical research in general, and the moxidectin study(ies) planned in the area specifically.

This information will not be provided with the objective of this information being published or for the purpose of participant recruitment but only for the benefit of education of the local media staff. Informing the local media (including new staff coming on board during study conduct) was proven helpful in the moxidectin Phase III study to reduce the possibility of incorrect information (rumors) being distributed in the study area.

5.4 Consultations with Religious, Village/Community Leaders, and Elders

As per local customs informing village/community leaders and elders, religious leaders and leaders of subgroups (e.g. youth groups) about the study will precede any contact with the villagers. Their guidance will be sought on:

- How to organize the study conduct and who should be involved in discussions on study conduct organization (including set up of areas where individuals can be examined in privacy);
- How to inform community members about onchocerciasis and the study planned in the area; and
- Suggestions from them for any other topic related to study conduct.

The agreement and support for village community meetings (or meetings with subgroups) will be obtained from the village/community leaders and elders before community meetings are held.

5.5 Consultation with Village Communities

5.5.1 Cultural and Socio-economic Characteristics of the Population from which Participants will be Recruited

The cultural and socio-economic characteristics of the population from which participants will be recruited are provided in the Attachment: Country-specific Information.

5.5.2 Community Meetings

After approval of the protocol and Participant Information Documents and Informed Consent/Assent Forms (PICF) by the country RA and EC and the WHO ERC (Section 15.2; Section 15.3; Section 15.9) and in consultation with village leaders and elders (Section 5.4), two community meetings will be held in the villages from which participants are planned to be recruited to which villagers ≥12 years will be invited.

The objective of the first meeting will be to inform the villagers about onchocerciasis, current onchocerciasis control strategies, information about moxidectin already available, the plan and rationale for conducting this study and the requirements for study conduct. Details provided on study will be limited to those required to obtain community input into the implementation plans including:

- Identification of location(s) where study procedures can be conducted in privacy;
- Selection of community members already involved in implementation of public health system measures and possibly other community members willing to be SFP (Section 5.2.4), i.e. to serve as conduit for questions, suggestions or complaints study participants may prefer not to address directly to the study team, remind villagers of upcoming follow up visits, support villagers in contacting the study team or local health facilities in case of AEs, and any other roles the villagers consider useful;
- Selection of literate witnesses for informed consent and assent with parental consent (Section 15.9);
- Planning for the next community meeting to inform the villagers about details of the study and discuss these with them;
- Any other study related topics the villagers want to discuss.

If villagers indicate that they would like their village to be included among the villages from which study participants are to be recruited, a second community meeting will be arranged to which again villagers ≥12 years will be invited. The objectives of this second community meeting will be to:

- Inform the participants about and discuss with them all details of the studies they need to have to decide whether or not they want to give written informed consent or assent with parental/guardian consent to study participation;
- Arrange meetings between community members interested in participation in one or the other study and study team members for further discussion of the details of the studies.

The information to be provided in both meetings is included in the PICF submitted to the ECs. During each meeting the relevant section of the PICF will be read and discussed paragraph by paragraph in the local language.

6 STUDY PARTICIPANT POPULATION

6.1 Participant Recruitment and Retention

The Attachment: Country-specific Information provides details on the selected study areas and Section 5 provides details on the activities that will precede participant recruitment.

The process for identifying individuals willing to participate in Screening and, if eligible, willing to participate in the study is described below.

The main retention strategy will consist of implementation of lessons learnt from public health programs, the Phase III study and other research studies:

- Ensuring that the communities from which participants will be recruited are engaged in study preparation and implementation;
- Treating participants with the respect they deserve as 'partners', not 'subjects' in this research (which includes e.g. provisions such as the SFP that allow the study team to quickly learn about and respond to questions and concerns); and
- Maintaining communication with participants via the trained site staff and SFPs, including about the importance of attending the follow-up visits organized in their villages.

6.2 Informed Consent and Assent with Parental/Guardian Consent

The principles guiding obtaining informed consent and assent from minors with parental/guardian consent (subsequently referred to as consent/assent) are described in Section 15.9.

The amount of information potential participants need to understand before deciding on study participation for themselves and/or their children/ward is substantial. Therefore, the information document is written in language considered suitable for 12 year old adolescents, allowing adults and adolescents to be informed simultaneously.

In one site in DRC (Ituri), recruitment for this study will be initially conducted concurrently with recruitment into the study evaluating the efficacy and safety of multiple annual and biannual treatment with moxidectin and ivermectin (study 3001, Section 2.4). The special provisions for concurrent recruitment are provided in the Attachment: Country-specific Information for DRC and in the protocol for study 3001.

Following approval of the study by the relevant RAs and ECs, the study team will initiate the community meetings described in Section 5.5.2.

The 2nd meeting to which villagers ≥ 12 years old will be invited and which will be attended by the witnesses the community chose during the first meeting, is the first step in recruitment:

- The section of the approved participant information document designed for this 2nd community meeting will be read and discussed in the local language paragraph by paragraph. This will allow all to benefit from answers to questions others are asking;
- Meeting participants will then be asked to approach study team members for further information and discussion in the presence of the selected witness if they are interested in participation;
- Those who continue to be interested in participating after having had adequate time to consider the study information and tell the study team members they want to participate, will be asked specific questions included in the EC approved PICF

to confirm their understanding of key screening and study elements in the presence of the selected witness (Section 5.5.2, Section 15.9.1). These questions are not meant as a 'pass-fail test' but to allow the team to identify key elements of consent/assent that require further discussion with the participant and/or parent(s)/guardian before they can provide informed consent/assent.

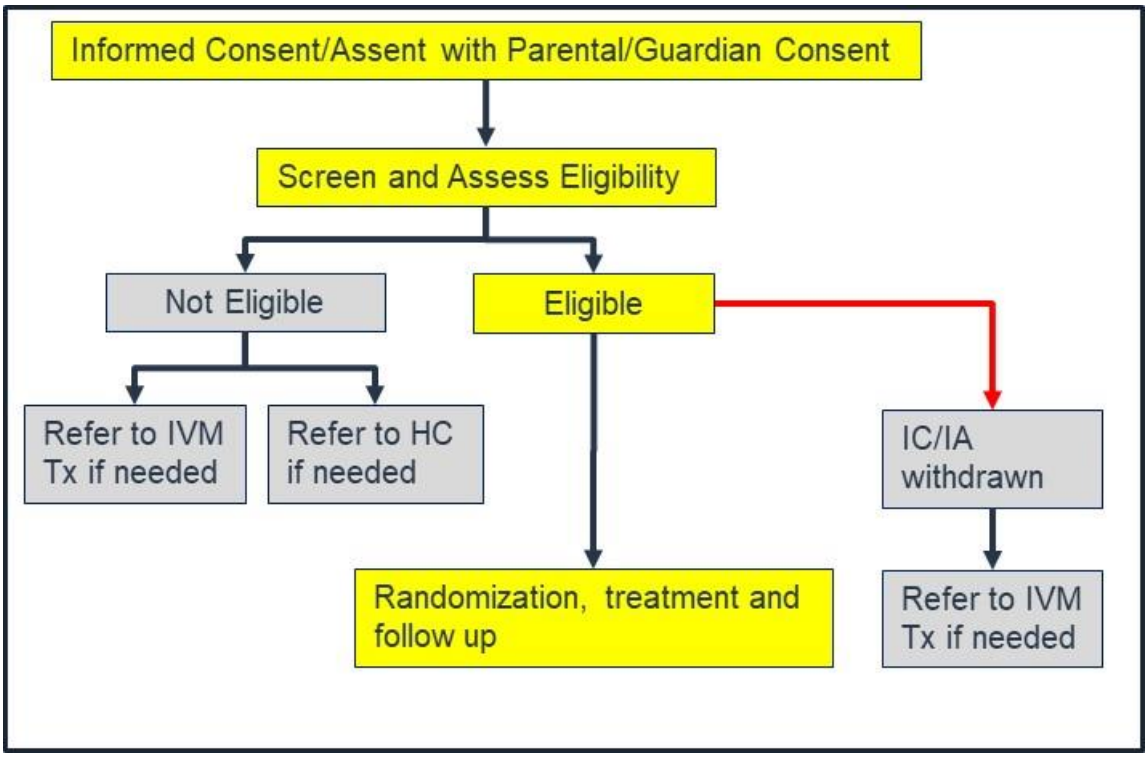
- Subsequently, the potential participant and, if applicable, his/her parents(s)/guardian will provide written informed consent/assent with parental/guardian consent which will be confirmed by the witness.

Individuals who have signed or finger printed/marked and dated the written informed consent/assent will be assigned a participant code and invited to attend screening.

See Section 15.9 for further information on the informed consent process, including for illiterate participants and minors.

The results of Screening will be presented to each individual (and parents/guardian, if applicable). If applicable, the reasons why they are not eligible for the study will be discussed with them and they will be referred to the local health care system if needed (Section 6.5, Figure 2).

Figure 2: Overview of participant flow following consent/assent with parental/guardian consent



HC = Health center/health facility; IC/IA = Informed consent/assent with parental/guardian consent; IVM = Ivermectin; Tx = treatment

6.3 Eligibility Criteria

Study participants must satisfy all eligibility criteria to participate. There will be no exemptions. Inclusion and exclusion criteria are to be determined at Screening unless otherwise indicated.

6.3.1 Inclusion Criteria

The criteria for entry into the study are:

1. Provision of written informed consent, or assent with parental or guardian written consent.
2. Known *O. volvulus* skin microfilariae density ≥0 microfilariae/mg skin
3. Living in an onchocerciasis endemic area.
4. Age ≥ 12 years.
5. All female participants of childbearing potential must commit to the use of a reliable method of birth control until 3 months after administration of investigational product (Month 3).

Following identification of a dose for children 8 to 11 years old and 4 to 7 years old in the paediatric study (Section 2.4) and upon recommendation of the DSMB (Section 12) and approval of the relevant protocol amendment and Information Documents by the responsible RA and EC, the lower age for inclusion may be reduced to include 8 to 11 year old and 4 to 7 year old children. For children 4 to 11 years old, skin snips will be optional, i.e. these children and their parents will choose whether they want skin snips to be taken and confirm their choice during assent and parental/guardian consent.

6.3.2 Exclusion Criteria

The criteria for exclusion from the study are:

1. Pregnant or breast-feeding.
2. Any concurrent condition that, in the opinion of the Investigator, would preclude evaluation of response to treatment or would pose undue risk to the participant's health.
3. Has received ivermectin or oral diethylcarbamazine (DEC) within 30 days of Baseline.
4. Has received treatment with an investigational agent within the last 30 days (or 5 half-lives, whichever is longer) prior to planned investigational product administration.
5. Known or suspected allergy to ivermectin or moxidectin or their excipients.
6. Self-reported planned or ongoing activities within the study period that would make it unlikely that the participant will be available for follow-up examinations.
7. Infection with *Loa loa*.

6.4 Other Eligibility Considerations

In order to assess any potential impact of a concurrent condition identified during Screening on participant eligibility and/or the safety of potential study participants, the Investigator must refer to the information on adverse reactions, precautions and warnings outlined in Section 10.5 and the documents referenced in that section (and reviewed at the initiation visit, see Section 15.6).

6.4.1 Pregnant and Breastfeeding Women

As no adequate and well-controlled studies of moxidectin or ivermectin in pregnant women have been conducted, the safety of moxidectin or ivermectin in pregnancy has not been

established (information available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf , http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Consequently, girls and women of childbearing potential must undergo a pregnancy test (Section 7.4.5) and must commit to using a reliable method of birth control until 3 months after investigational product administration. Women of childbearing potential who withdraw from the study within 3 months of investigational product administration should be advised to avoid becoming pregnant until 3 months after investigational product administration.

All girls and women of childbearing potential will be counselled on reliable methods of birth control (including abstinence) and available contraceptive measures as recommended by the local maternal or reproductive health or family planning program (as applicable). The chosen contraceptives will be made available by the Sponsor free of charge.

For participants not choosing abstinence, reliable methods (failure rate of less than 1% when used consistently and correctly) of contraception will be those offered by the maternal or reproductive health or family planning program (as applicable) and may include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- progestogen-only hormonal contraception associated with inhibition of ovulation,
- intrauterine device;

A pregnancy test will be conducted at Month 3.

Study staff counselling women on contraception will have the relevant experience.

Women who are not of childbearing potential (before menarche or those who have been postmenopausal for at least 12 consecutive months without alternative medical cause or have undergone hysterectomy, bilateral oophorectomy or tubal ligation) are not required to undergo pregnancy testing or to commit to contraception.

A study in lactating, non-breastfeeding women (Study 1002) showed that after a single dose of 8 mg moxidectin, it was present in the breast milk at a relative infant dose of less than 10% of the maternal dose (Korth-Bradley et al. 2011). There is currently insufficient data on the potential risk of moxidectin exposure for the breastfeeding infant.

For ivermectin, the US FDA approved prescribing information advises that ivermectin is excreted in human milk in low concentrations and that treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf , http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Consequently, women who are breast-feeding are not eligible for the study.

6.4.2 *Loa loa* Infection

Individuals heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma.

Moxidectin has not been tested in individuals infected with *Loa loa*.

Consequently, the study areas selected for this study are not *Loa loa* co-endemic. Individuals will be asked about their exposure to *Loa loa* endemic areas. Those reporting a history of living or working or still temporarily working in *Loa loa* endemic areas or symptoms suggestive of *Loa loa* infection (e.g. eye worm) will undergo screening for loiasis (Sections 7.3.1 and 7.4.7).

6.5 Referral of Individuals Not Eligible for Study Participation

Individuals identified as *O. volvulus* infected by skin snip but not qualifying for or willing to participate in this study will be given referral information for the local health system/ onchocerciasis control program for ivermectin treatment if community-directed treatment with ivermectin is not implemented in their village or else be advised to participate in each community-directed treatment with ivermectin round.

Individuals not eligible for study participation because of a health condition requiring medical attention will be given referral information for the local health system.

Individuals not eligible for participation because of *Loa loa* infection will be provided with a written note to that effect for presentation at future community directed treatment with ivermectin campaigns so that national program mandated precautions for the treatment of these individuals can be taken as per national guidelines.

6.6 Rescreening

Individuals may be rescreened once under a new participant code if, in the opinion of the Investigator, the eligibility criteria are likely to be met upon rescreening.

7 SCHEDULE OF ASSESSMENTS AND PROCEDURES

7.1 Study Schedule of Evaluations

The schedule of assessments is presented in Table 1.

7.2 Visit Windows

The Baseline visit must occur within the 30 days after Screening.

The assessments on Days 1 to 5 after investigational product administration must occur on the specified days.

There is a plus or minus one-month window for the Month 3 visit.

7.3 Study Procedures

The study procedures to be conducted for each individual participating in the study are listed below. The results will be documented in the source records and, as required, entered or uploaded into the eCRF (Section 16.1 and Section 16.2).

No study procedures will be conducted prior to the provision of the relevant written informed consent/assent. Unless otherwise indicated, all procedures will be conducted in the villages in a private place set up as agreed with village communities (see Section 5.4 and Section 5.5.2).

Additional detail on study procedures is provided in Section 7.4.

Any deviation from study procedures will be noted in the source records and eCRF, as required, and the Sponsor will be notified.

After each visit, participants will be informed about the results obtained.

7.3.1 Screening (Day -30 to Day -1)

Following the provision of written informed consent/assent, the following procedures will be undertaken to determine eligibility.

- Demography (date of birth and sex, history of living or working or still temporarily working in loiasis endemic areas) (Section 7.4.1);
- Medical history (pre-existing medical conditions or surgical history, and potential history of *Loa loa* infection/eye worm);
- Prior and concurrent medication (Section 9);
- A complete physical examination (Section 7.4.3);
- Body weight and height (Section 7.4.4);
- A urine pregnancy test for women and girls of childbearing potential (Section 7.4.5);
- Calibrated blood smear for determination of *Loa loa* infection in individuals who have lived or worked or still temporarily working in loiasis endemic areas and/or who report symptoms suggestive of *Loa loa* infection (Section 7.4.7); and
- Collection of two skin snips (one from each iliac crest) for assessment of skin microfilariae density (Section 7.4.6).
- AE assessment (Section 10);

- Where the Add-on evaluation of the DEC-Patch is conducted: Application of the DEC-Patch, removal approximately 24 hours later, assessment of the skin underneath the DEC-Patch area and evaluation for adverse events (Section 7.4.10).

7.3.2 Randomization and Investigational Product Preparation

For all participants who meet all the inclusion criteria and none of the exclusion criteria, and have given informed consent/assent to study participation, randomization and investigational product preparation will occur as described in Section 8.1 and Section 8.6.

7.3.3 Baseline and Confirmation of Eligibility (Day – 1 to 0)

Where the Add-on evaluation of the DEC-Patch is conducted and the DEC-Patch is applied only on Day -1: patch removal and assessment of the skin underneath the DEC-Patch area and evaluation for adverse events will occur on Day 0 before investigational product administration (Section 7.4.10)

To confirm eligibility, and/or obtain up to date baseline data, the following assessments will be performed, if required:

- If more than 1 day has passed between the Screening pregnancy test and planned investigational product administration:
    - Urine pregnancy test for women and girls of childbearing potential (Section 7.4.5); and
- If more than 3 days have passed between Screening and planned investigational product administration, or clinically indicated:
    - A targeted physical examination (based on previous findings and current symptoms or health issues that have occurred since Screening) (Section 7.4.3);
    - AE assessment (Section 10);
    - Concurrent medication review (Section 9).

7.3.4 Investigational Product Administration (Day 0)

Participants continuing to meet all the inclusion criteria and none of the exclusion criteria will be administered investigational product while being observed by study staff (Section 8.6).

Any investigational product dispensed but not administered will be returned to the Pharmacy and accounted for as described in Section 8.7.

7.3.5 Daily Assessments after Investigational Product Administration (Days 1 to 5)

For the first five days after investigational product administration, the following assessments will be conducted:

- AE assessment (Section 10);
- concurrent medication assessment (Section 9);
- a targeted physical examination (based on symptoms) (Section 7.4.3).

Should the participant experience discomfort or signs and symptoms of the Mazzotti reaction, or other adverse events, treatment should be provided if requested by the participant or considered clinically indicated (see Section 10.5). Any medication provided by the study team or in a local health center (see Section 9) must be documented and reported in the source records and eCRF together with the indication for which it was provided.

Additional follow-up visits will be scheduled should they be indicated for appropriate follow-up of AEs and recorded in the source records and eCRF as unscheduled visits.

7.3.6 End of Study Visit (Month 3)

Each participant will be assessed at Month 3 (± 1 months).

The following assessments will be performed as indicated and documented in the source records and eCRF:

- AE assessment (Section 10);
- Concurrent medication assessment (Section 9);
- A targeted physical examination (based on symptoms) (Section 7.4.3); and
- Urine pregnancy test for women and girls of childbearing potential (Section 7.4.5)

7.3.7 Exit Examination at Early Withdrawal or Early Study Termination

Participants have the right to withdraw from the study at any time for any reason (see Section 13.2) and without giving any reason for the decision to do so, or may be withdrawn by the investigator (for criteria for withdrawal from the study and follow up, see Section 13.2).

Study team members will attempt to visit each participant who withdraws or is withdrawn. The reason for withdrawal should be recorded, including, if applicable, that the participant prefers not to provide a reason or could not be reached.

If permitted by the participant, an exit examination should be conducted as close as possible to 3 months after investigational product administration to allow evaluation for investigational product related adverse events (for further information on the rationale for this examination see Section 13.2.2), or at another time of the participant's choosing and include the following:

- AE assessment (Section 10), including need for further follow-up;
- Concurrent medication assessment (Section 9);
- A targeted physical examination (based on symptoms) (Section 7.4.3); and
- Urine pregnancy test for women and girls of childbearing potential (Section 7.4.5).

This exit examination will also be performed in case of early termination of the study for all study participants who have not yet had a Month 3 evaluation (Sections 13.5 and 13.6).

7.4 Details of Scheduled Assessments

The results of all assessments will be recorded in the source records. On the source records (Section 16.1), participant will be identified via their participant code as well as their initials and/or names.

As required, data from the source records will be entered or uploaded to the eCRF (Section 16.1 and Section 16.2). In the eCRF, study participants will be identified only by their participant code, not their name or initials to ensure participant confidentiality.

Confidential screening logs will be completed with details of both participant codes and participant names (Section 16.3).

The following provides details of the assessments to be undertaken. Scheduling of assessments is described in Section 7.3 and Table 1.

7.4.1 Demography

Demographic data includes sex, date of birth, and history of living or working or still temporarily working in an area(s) where *Loa loa* is endemic.

7.4.2 Medical History, Concurrent Conditions and Prior and Concurrent Medications

This will include any past or current medical conditions or surgical history, prior and concurrent medication, and questioning about a potential history of *Loa loa* infection (eye worm).

7.4.3 Physical Examination

A complete physical examination (including head, ears, nose, throat, lungs, lymph nodes, heart, abdomen and skin) will be conducted at the Screening visit to determine study eligibility. Abnormalities will be recorded.

At all other visits, a targeted physical examination will be performed as clinically indicated guided by symptoms.

Any new abnormalities or worsening of screening conditions detected during physical examinations must be recorded as AEs (see Section 10 for details).

Signs and symptoms of onchocerciasis identified during medical history taking or physical examination that worsen or re-emerge after treatment must also be reported as AEs (see Section 10 for details).

7.4.4 Weight and Height

Height will be measured in centimeters (cm) without shoes.

Weight will be measured in kilograms (kg) wearing light clothing without shoes.

7.4.5 Pregnancy Test

A β-HCG urine pregnancy test will be performed for women and girls of childbearing potential before investigational product administration. They will be instructed by the study staff in how to collect a urine sample for testing.

Upon completion of the pregnancy test, study staff will review the result to confirm that the woman is not pregnant prior to proceeding to administration of investigational product.

Pregnancy does not require withdrawal from the study unless the participant elects to withdraw, or the Investigator decides that the participant should be withdrawn in the interest of her health and pregnancy. Sections 10.6 and 13.2 provide details on follow up of pregnancies.

Provided the participant has given informed consent/assent to this, urine remaining from these samples may be stored frozen for potential future use (Sections 15.19 and 15.20.2 and Attachment: Country-specific Information).

7.4.6 Quantification of Skin Microfilariae Density

Two skin snips will be taken (one from each of the left and right iliac crest) using a 2 mm Holth-type corneoscleral punch after cleansing the snip sites with 70% alcohol.

Punches will be steam-sterilized before use on the next individual.

Briefly, each snip will be weighed and incubated for at least 8 hours in isotonic saline. The microfilariae that have emerged from the skin snip will be counted in each well using an inverted microscope. At Screening, the mean mf/mg across the two skin snips will be calculated to determine the participant randomization stratum (< 20 mf/mg skin vs. ≥ 20 mf/mg skin, Section 8.1).

Microfilariae will be preserved in alcohol after counting, for future use (Section 15.19).

If microfilariae of *Mansonella streptocerca* are present in the skin specimen (identified visually on microscopy), their number will be noted on the source records but not collected in the participant's eCRF.

7.4.7 Diagnosis of *Loa loa* Infection

Individuals with a history of living or working or still temporarily working in an area where *Loa loa* is endemic or with a history of eye worm or other symptoms suggestive of *Loa loa* infection will undergo a test for *Loa loa* infection. For these participants, diagnosis of *Loa loa* infection will be performed via calibrated blood smear. Briefly, blood will be collected (between approximately 11:00 and 14:00 hours) by finger prick with a 60 µL non-heparinized capillary tube, after careful cleaning of the finger. The blood will be spread on a labeled slide, dried and Giemsa stained and dried at ambient temperature. All *Loa loa* microfilariae on the slide will be counted at a magnification of 100x.

If *Loa loa* microfilariae are present, the number of parasites will be recorded in source records and the individual will be excluded from the study.

7.4.8 Vital Signs

If measurement of vital signs is indicated, they should be measured after the participant has been semi-supine for 5 minutes and recorded with the following units:

- Body temperature (degrees Celsius [°C]);
- Respiratory rate (breaths per minute);
- Pulse rate (beats per minute); and
- Blood pressure (millimeters of mercury [mmHg]).

If abnormally high or low blood pressure is observed, two further measurements, taken 5 minutes apart should be performed and recorded.

7.4.9 Collection and Processing of Biological Specimens

Skin, blood and urine specimens collected during the trial may contain harmful pathogens. All personnel involved in collecting and handling biological specimens will be trained on Prevention and Control of Infection (PCI) in order to be able to implement appropriate precautionary procedures for handling biohazardous materials as currently recommended by the WHO Emerging and Communicable Diseases, Surveillance and Control Guidelines (World Health Organization 1997) or relevant updates or country guidance. The processing of all biological specimens will be in accordance with relevant SOPs and as required for the objectives of their collection, as described above.

For storage, ownership and future use of left over *O. volvulus* parasites and urine left over from pregnancy tests, see Sections 15.19 and 15.20 and Attachment: Country-specific Information.

7.4.10 DEC-Patch Evaluation during Screening

After cleaning of the skin by swabbing with 70% methylated spirit and letting it dry, the DEC-Patch will be applied to the iliac crest and light pressure applied for 10 seconds and the DEC-Patch further secured with a plaster.

The patch will be removed after approximately 24 hours and the skin underneath the patch examined for the diagnostic skin reaction. The intensity of the skin reaction will be scored according to the criteria described by Awadzi et al. 2015 by two readers independently. If the two readers do not agree, each score will be recorded in the source records and the

readers will examine the reaction jointly and the agreed upon score will be documented in the source records. All scores will be recorded in the eCRF.

At the time of the reading of the skin reaction, participants will be asked about any AEs they experienced since the DEC-Patch application, and whether the patch had detached and if so, the approximate time of detachment. The AEs will be graded and assessed for relationship to DEC-Patch application according to the criteria described in Section 10.2.2.

For further information, see Attachment: Country-specific Information

8 INVESTIGATIONAL MEDICINAL PRODUCT

In this study investigational medicinal products are moxidectin and ivermectin without or with placebo.

8.1 Randomization and Treatment Allocation

The randomization code will be generated using computer-generated random treatment allocations with randomly permuted blocks, which may include random block sizes. Each block of sequential numbers will include in random order moxidectin and ivermectin treatment allocations, reflective of the 4:1 treatment allocation planned for this study (Section 4.3).

The randomization will be stratified at each site by Screening skin microfilariae density (< 20 mf/mg skin or ≥ 20 mf/mg skin). Each site will have its own set of randomization lists. Depending on the size of the geographic area over which a particular site will be recruiting participants, additional stratification by an appropriate geographic area-defining criterion (e.g. Aire de Santé) may be introduced for that site.

Individuals found to be eligible for study participation will be allocated the next available number in sequential order, from lowest to highest, on the randomization list for their Screening skin microfilariae density stratum (and Aire de Santé, if applicable). The staff randomizing participants will not be involved in participant follow up.

The randomization algorithm will be generated by an independent statistician not otherwise participating in the study. A separate document outlining the specifics of the randomization algorithm will be prepared and available upon study completion.

8.2 Blinding

The study will be conducted as a double-blind study. To maintain the blind, each participant will receive four matching capsules prepared by unblinded staff authorized to dispense drugs by national law and who will not be involved in participant assessment. Neither the participants nor staff involved in their follow up or examination of participant samples will know which treatment a study participant received.

8.3 Unblinding

The Investigator has the right to break the blind or authorize a study team member to break the blind when knowledge of the study treatment is considered important for optimal medical management of a participant. For this purpose, sealed envelopes (or equivalent) with the treatment assigned to each randomization number will be held at the site by the Investigator (or delegate). Duplicate envelopes (or equivalent) will be held by the Sponsor/Medical Monitor.

Wherever possible without jeopardizing participant safety, the Investigator should discuss the intention to break the blind with the Medical Monitor before breaking the blind. The final decision rests with the Investigator.

If the code is broken, the envelope must be signed and dated on both seals by the code breaker. The individual name and signature of the code breaker, and date and time of the code break needs to be recorded on the outside of the envelope. Information must be entered into the participant's source records and the relevant eCRF page, explaining the reason and date that the sealed envelope was opened. This must be countersigned by the Investigator.

The Investigator must notify the Sponsor/Medical Monitor by email at sae@medicinesdevelopment.com or if that is not feasible, via telephone (+61 409 020 209) within 24 hours after having broken the blind including the participant code, randomization

number and the circumstances leading to the decision to unblind. Furthermore, the Investigator must provide a written report of the event to the Sponsor within five working days.

8.4 Formulation

The investigational products to be administered in this clinical trial are encapsulated moxidectin tablets, 2 mg (manufactured by MDGH) and ivermectin tablets, 3 mg (manufactured by Edenbridge LLC).

Moxidectin tablets contain 2 mg of moxidectin supplied as 100 mg white to pale yellow, uncoated, oval-shaped tablets. Moxidectin tablet components are provided in Table 4.

Table 4: Moxidectin Tablet Components

Component	Quality Reference	Function
Micronized moxidectin	United States Pharmacopeia	Active ingredient
Microcrystalline cellulose	US Pharmacopeia National Formulary	Diluent
Lactose, anhydrous	US Pharmacopeia National Formulary	Diluent
Sodium lauryl sulfate	US Pharmacopeia National Formulary	Surfactant
Colloidal silicon dioxide	US Pharmacopeia National Formulary	Glidant
Croscarmellose sodium	US Pharmacopeia National Formulary	Disintegrant
Magnesium stearate	US Pharmacopeia National Formulary	Lubricant

Ivermectin will be a 3 mg tablet (US Authorized product National Drug Code NDC 42799-806-01) containing the ingredients as per Table 5.

Table 5: Ivermectin Tablet Components

Component	Function
Ivermectin 3 mg	Active ingredient
Microcrystalline cellulose	Inactive
Pregelatinized starch	Inactive
Magnesium stearate	Inactive
Colloidal silicon dioxide	Inactive
Croscarmellose sodium	Inactive

Each moxidectin or ivermectin tablet will be overencapsulated in a Size #1, opaque, white, hypromellose (hydroxypropyl methylcellulose, HPMC) hard shell capsule. Each capsule will be backfilled with inert excipient powder (microcrystalline cellulose).

Matching placebo capsules will be filled with the same inert excipient powder.

8.5 Supply, Packaging and Labelling, Storage and Handling

Investigational product will be supplied by the Sponsor as moxidectin 2 mg in capsules, ivermectin 3 mg in capsules, or placebo capsules. The investigational product will be supplied in white high-density polyethylene bottles with a polypropylene closure and induction seal, a pharmaceutical coil (filler) and silica gel desiccant sachet.

Investigational product will be shipped to the site after receipt of required documentation of study approval and in accordance with applicable regulatory requirements.

The Investigator or authorized designee will ensure that the investigational product is stored below 25°C and protected from light and moisture in a secure area with access limited to authorized staff, and according to relevant regulations. The capsules must not be frozen or stored at temperatures above 30°C. Temperature excursions are permitted up to 30°C for up to 12 months.

Labelling of the bottles with moxidectin in capsules, with ivermectin in capsules or with placebo-to-match capsules will be in accordance with local regulations and as approved by the national RA and will include at a minimum:

- Sponsor name;
- Protocol number;
- Product name;
- Product strength;
- Route of administration;
- Lot number;
- Expiry date or retest date; and
- 'For Clinical Trial Use Only'.

8.6 Dosage and Administration

After randomization and determination of the regimen to which the participant is allocated, a dose of investigational product will be dispensed.

Dispensed investigational product will be administered only to participants confirmed to be eligible on Day -1 to Day 0.

Participants will swallow the investigational product with water under the direct observation of study staff.

8.6.1 Moxidectin

The dosing of moxidectin does not depend on participant weight or height.

Participants randomized to moxidectin will receive four moxidectin capsules.

8.6.2 Ivermectin

Ivermectin is provided as 3 mg tablets and dosing is weight-based (150 μg/kg) as per Prescribing Information (available at https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

However, weight-based dosing is challenging during mass ivermectin administration and APOC had provided guidance to onchocerciasis endemic country programs on height-based dosing criteria (Table 6) (World Health Organization and African Programme for Onchocerciasis Control 1998). To obtain safety data after ivermectin treatment with dosing comparable to that used by control and elimination programs, these criteria will be used in this study.

Table 6: Height Based Ivermectin Dosing Schedule

Height	Number of capsules with 3 mg ivermectin tablets (as per APOC guidance)	Number of placebo capsules to ensure blinding
90 cm to 119 cm	1	3
120 cm to 139 cm	2	2
140 cm to 159 cm	3	1
> 159 cm	4	0

8.7 Dispensing and Accountability

The Investigator is responsible for ensuring that the investigational product is dispensed in accordance with the protocol. Only individuals authorized as per the applicable national law to dispense drugs and by the investigator will dispense investigational product.

For each participant, the investigational product corresponding to their randomized treatment allocation will be prepared.

The date of investigational product preparation, participant code, randomization code and the number and types of capsules dispensed must be recorded in the Drug Dispensing and Accountability log provided for the study.

Any investigational product dispensed but not administered to a participant must be recorded in the log and the unused capsules stored in a separate container, appropriately labelled, for accountability review by the unblinded Study Monitor.

The Investigator will be responsible for ensuring accurate records are maintained for all investigational products received, dispensed, dispensed and not administered, returned or destroyed. The inventory and dispensing logs must be available for inspection by the unblinded Study Monitor. Investigational product supplies, including partially used or empty bottles, and dispensed and not administered investigational product must be accounted for by the unblinded Study Monitor and returned to the Sponsor for destruction at the end of the study. Copies of the records of investigational product returned to the Sponsor must be retained by the Investigator.

As required by national law and in consultation with the Sponsor, unused investigational product supplies may be destroyed locally consistent with the local regulations. Copies of records on the destroyed investigational product shall be retained by the Investigator. These records must show the identification and quantity of each investigational product capsule disposed of, the method of destruction, and the person who disposed of the investigational product. Copies of such records shall be submitted to the Sponsor.

8.8 Shipment of Investigational Medicinal Product

Investigational product will be shipped to the site only after export is permitted from the US, an import permit into the study country has been received by the Sponsor and the Sponsor has confirmed that all relevant authorizations and Sponsor documentation requirements for the study have been met. Shipment of investigational product may occur before the Site Initiation Visit with secure storage at the site under quarantine, until the study has been initiated.

9 CONCURRENT MEDICATIONS

At each study visit or contact, the Investigator should ask the participant about any concurrent medications or medications taken since the previous visit or contact.

All concurrent medications, including any traditional medicines as well as traditional or religious interventions (such as spiritual exorcism), must be recorded in the appropriate section of the source records and eCRF, including start and stop date, dose and dosing indication.

9.1 Special Dietary Requirements

There are no special dietary requirements during the study.

9.2 Prohibited Concurrent Medications

Throughout the study, participants should not receive any of the following medications without a physician having determined that this medication is necessary for the health of the participant:

- Anti-onchocercal treatments including ivermectin, oral DEC;
- Doxycycline for a duration of more than 2 weeks; and
- Other investigational products for non-life threatening conditions.

In case of non-compliance, the prohibited concurrent medication taken should be documented in the source records and the information requested on the concomitant medication page of the eCRF should be completed.

9.3 Permitted Investigational Products

In the interest of the health of study participants, as well as potentially public health, investigational products for life threatening conditions are permitted for which no or insufficient effective and safe treatments or vaccines are available. This includes, but is not necessarily limited to, Ebola Virus Disease Vaccination.

The Ebola Virus vaccine rVSVΔGP-ZEBOV-GP (ERVEBO, Merck&Co, Inc.) has been prequalified by WHO (World Health Organization. 2020) and received conditional marketing authorization by the European Medicines Agency in November 2019 (European Medicines Agency. 2020).

Ring vaccination with rVSVΔGP-ZEBOV-GP is deployed at large scale by the Ministère de la Santé publique (MdSP) for control of the outbreak in Nord Kivu and Ituri. Thus, its use is authorized by the MdSP outside clinical trials. Consequently, and in the interest of the health of study participants, their communities and public health, rVSVΔGP-ZEBOV-GP is not considered an investigational product in this protocol and consequently rVSVΔGP-ZEBOV-GP vaccination is permitted.

Applications for European Medicines Agency approval have been submitted for each of the two components of another Ebola Virus vaccine consisting of a dose of Ad26.ZEBOV followed by a dose of MVA-BN-Filo and are undergoing Accelerated Assessment. The MdSP of DRC has authorized use of this vaccine within a Phase III study in North Kivu in DRC (https://clinicaltrials.gov/ct2/show/NCT04152486). Should this or subsequent studies, or MdSP authorized deployment of this vaccine, be implemented in the area where MDGH-MOX-3002 is being conducted, participants may receive this vaccine.

The study team will coordinate assessment activities for this study and the vaccine study with the staff involved in the evaluation of the vaccine.

For other countries in which study 3002 will be conducted, the same provisions will apply in case of an Ebola Virus Disease outbreak and country Ministry of Health approved deployment of Ebola Virus Disease vaccines outside or within a clinical trial.

Vaccination will be documented in the source records and eCRF as required for all concomitant medication.

10 ADVERSE EVENTS AND MANAGEMENT

10.1 Safety Assessments

Safety assessments will include physical examinations, questioning participants for AEs, concomitant treatments (pharmacological or non-pharmacological), and any clinically indicated examinations (e.g. vital signs).

10.2 Adverse Events

10.2.1 Adverse Event Definition

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an AE is any untoward medical occurrence in a clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

Pre-existing signs, symptoms, or diseases, which increase in frequency or severity or change in nature following administration of the investigational product, are also considered an AE.

Post-treatment complications that occur or worsen as a result of protocol-mandated procedures (e.g. as a result of skin snips) are also AEs.

AEs as per ICH definition are referred to as 'Treatment Emergent Adverse Events' (TEAE).

In addition to the events defined as AE by the ICH, any a new event or an exacerbation of a pre-existing condition or complication from a protocol mandated procedure with onset after written informed consent/assent up to the investigational product administration will also be recorded in the source records and reported as an AE on the appropriate eCRF page(s).

The following are **not** AEs:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); in contrast, the condition that leads to the procedure is an AE if it started or worsened after informed consent/assent but not if it was present before informed consent/assent;
- Pre-existing diseases or conditions (i.e. present prior to informed consent/assent), that do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, or overnight stays in a health care facility or the research center for social and/or convenience reasons e.g. because of road conditions it is not considered safe to transport the participant back to the home village at night); and
- Overdose of either investigational product or concomitant medication without any signs or symptoms, unless the participant is hospitalized for observation.

10.2.2 Grading of Severity of Adverse Events and Evaluation of Relationship to Investigational Product

All AEs will be assessed by the Investigator and recorded in the source records and on the appropriate eCRF page, including the date of onset and resolution, severity, relationship to investigational product, outcome and action taken including regarding investigational product administration.

Each AE will be graded for severity using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (Appendix 1: Adverse Events Toxicity Grading Scale). For AEs not specifically described in the DAIDS grading scale, the grades presented in Table 7 should be applied.

Table 7: Adverse Event Severity Assessments for Events not Included in the DAIDS Table

Grade	Severity	For CLINICAL events not otherwise described in the DAIDS AE grading table, the following descriptions of severity apply
1	Mild	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.
2	Moderate	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention.
3	Severe	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
4	Potentially life-threatening	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The relationship to investigational product should be assessed using the following definitions (Table 8).

Table 8: Investigational Product Causality Assessments

Causality	Comment
Unrelated	AE is clearly due to extraneous causes (e.g. underlying disease, environment, known effect of another drug).
Unlikely	The temporal association between the AE and investigational product is such that investigational product is not likely to have any reasonable association with the AE.
Possible	The AE could have been produced by the participant's clinical state or investigational product.
Probable	The AE follows a reasonable temporal sequence from the time of investigational product administration and cannot be reasonably explained by the known characteristics of the participant's clinical state.
Definite	The AE follows a reasonable temporal sequence from the time of investigational product administration, and/or reappears when investigational product is re-introduced.

10.2.3 Adverse Event Reporting

All AEs, regardless of severity, causality or seriousness (Section 10.3), and whether initially recorded at a local health center a participant may choose to go to (Section 5.2.3) or by a study team member during the protocol scheduled follow up visits or ad hoc visits at the request of a participant, must be reported from the date of written informed consent/assent up to the last day on study or for 3 months after investigational product administration, whichever is later.

This is required to obtain as comprehensive an AE data set as possible to support further characterization of the safety profile of moxidectin and ivermectin: a priori it is not possible to know which AEs may have a relationship to the study drugs and thus exclude some from collection/reporting. Participants will be informed about collection of data related to health problems they report to local health facilities during the discussions preceding Informed Consent/Assent with Parental/Guardian Consent. All AEs, whether initially recorded at a local health center or by a study team member are subject to the same confidentiality provisions (see Section 15.17 and Section 17).

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be

documented as the AE in the eCRF and, if applicable, reported as a SAE, and not the individual signs/symptoms recorded in the source documents.

10.3 Serious Adverse Events

10.3.1 Definition

A **serious adverse event** (SAE) is defined as any AE that results in any of the following outcomes:

- Death;
- Life-threatening situation (participant is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity; and/or
- Congenital anomaly/birth defect in the offspring of a participant who received investigational product.

Furthermore, the following are considered a SAE:

- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, if, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
  Examples of such events are:
  - intensive treatment in an emergency room or at home for allergic bronchospasm;
  - blood dyscrasias or convulsions that do not result in hospitalization; and/or
  - development of drug dependency or drug abuse.

10.3.2 Clarification of Serious Adverse Events Definition and Terminology

Death is an outcome of an AE, and not an AE in itself. In reports of death due to “Disease Progression”, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the investigational product.

“Life-threatening” means that the participant was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, that AE is a SAE.

“In-patient hospitalization” means the participant has been formally admitted to a hospital (or another type of health facility) for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department or an overnight stay at a hospital for 'social/convenience reasons' (i.e. the participant cannot be safely brought home at night).

10.3.3 Serious Adverse Event Reporting Requirements

10.3.3.1 SAE Reporting to the Sponsor

The Sponsor must be notified immediately about any SAE that occurs after the informed consent/assent has been obtained.

Study sites will be provided with internet access to ensure that SAE report forms can be sent expeditiously. If that is not feasible, notification will be via phone to the Medical Monitor until the SAE report forms can be sent electronically.

The procedures for reporting all SAEs occurring for participants until the last study visit, regardless of causal relationship and outcome, are as follows:

- Complete the "Serious Adverse Event Report" form; and
- Send the completed "Serious Adverse Event Report" form by email to the MDGH safety desk (sae@medicinesdevelopment.com), or as otherwise advised in writing by the Sponsor within 24 hours of the Investigator's knowledge of the event.
    - For fatal or life-threatening events, also send copies of hospital case reports, autopsy reports, and other documents when requested by the Safety Desk and available. Participant name and other participant identifying information on these documents must be obscured and the participant code added.
- Medical Monitor phone number for notification until reporting to the e-mail address is feasible: +61 409 020 209

Regardless of the cause, all deaths occurring up to the last study visit or 3 months after treatment, whichever is later, must be reported to the Sponsor within 24 hours of the Investigator's knowledge of the death to the e-mail address or phone number provided for SAE reporting.

The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports to the regulatory authorities. All additional information requested has to be sent anonymized and with the participant code added.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded in the source records and the concurrent medication section of the participant's eCRF.

A SAE may qualify for expedited reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the investigational product and is unexpected (Suspected Unexpected Serious Adverse Reaction (SUSAR)). An unexpected adverse reaction is defined by the ICH as 'An adverse reaction, the nature or severity of which is not consistent with the applicable product information'. The applicable product information for this study are the Investigator's Brochure for moxidectin and the Ivermectin Prescribing Information (available at www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf ; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

10.3.3.2 SAE Reporting to RA and EC

The Investigator will notify the RA and the EC of SAEs as per the reporting requirements specified in the RA and EC approval letters.

If the letters do not include specific requirements for expedited reporting of SAEs or SUSARs, all SAEs will be included in the Investigator's annual update to the EC and RA.

10.4 Follow Up of Serious and Non-Serious Adverse Events

Follow-up of serious and non-serious AEs will continue through to the last day on study. For participants completing the study, this will be the Month 3 visit.

If a participant withdraws early from the study, AEs will continue to be collected until 3 months after the dose of investigational product, if permitted by the participant.

The Sponsor may request that certain AEs be followed until resolution or until the Investigator and/or the Sponsor determine that the participant's condition is stable. For participants who have withdrawn from the study, their agreement is required.

Based on prior experience of treatment related AEs in the Phase II and Phase III clinical trials of moxidectin and ivermectin, it is anticipated that the majority of AEs will occur and resolve within the first five to six days after administration of investigational product without treatment (i.e. day of administration (Day 0) to 5 days later). In these previous studies, when treatment was provided, it was primarily administered for alleviation of symptoms such as itch or minor pain. To capture such AEs in this study, an appropriately trained member of the study team will visit each participant daily during the five days following investigational product administration (see Section 7.3.5). The need for treatment will be assessed and treatment provided as clinically indicated and treatment and the reason documented in the source records and eCRF.

For illnesses that are common in the study population and that occur while on study, for example malaria, respiratory infections, diarrhea, or conjunctivitis, the study team will in general provide appropriate treatment.

Else, and for other conditions not related to the investigational products or study procedures that occur on study and require hospital treatment or ongoing management (e.g. appendicitis, broken bones, snake bite, epileptic attacks), study participants will be referred to a local health clinic or hospital. Costs of treatment for conditions not possibly, probably or definitely related to investigational product or study conduct will not be covered by the study.

Study participants may prefer to visit local health care staff/clinic rather than to contact a study team member (directly or via the SFP in their village) in case of an AE they experience after Day 5 after treatment. As outlined in Section 5.2.3, collaborations with the local health care system will be set up to ensure that the study team is informed and can collect all AE and treatment data, as well as compensate the health system for treatment of all AEs possibly, probably or almost certainly related to treatment with investigational product, or due to a study procedure. This is included in the PICF.

10.5 Precautions for Treatment with Moxidectin or Ivermectin

For more information regarding precautions and AEs with ivermectin, the Investigator is referred to the Prescribing Information (available at https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

For more information regarding precautions and AEs with moxidectin, the Investigator is referred to the Prescribing Information (available at Drugs@FDA; www.fda.gov/drugsatfda) and the Investigator's Brochure.

Warnings and precautions associated with treatment of individuals with onchocerciasis with moxidectin or ivermectin are summarized below.

10.5.1 Adverse Reactions Associated with Moxidectin or Ivermectin

Treatment of *O. volvulus* infected individuals with moxidectin or ivermectin may cause cutaneous, ophthalmological, and/or systemic reactions of varying severity (Mazzotti reactions).

These adverse reactions are due to allergic and inflammatory host responses to the death of microfilariae following treatment. Just as with the signs and symptoms of onchocerciasis, there is both significant variability in the frequency and severity of these reactions between individuals and a trend toward an increased incidence and severity of some of these reactions in individuals with higher microfilarial burden.

Treatment of severe Mazzotti reactions has not been evaluated in controlled clinical trials. Symptomatic treatments such as oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat orthostatic hypotension. Antihistamines and/or analgesics have been used for most mild to moderate Mazzotti reaction cases.

10.5.1.1 Clinical, Ophthalmological and/or Systemic Adverse Reactions

The clinical manifestations of Mazzotti reactions include pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia.

An increased number of participants in the Phase III study who received moxidectin developed symptomatic orthostatic hypotension, with inability to stand without support, after lying down for at least 5 minutes in an orthostatic hypotension provocation test: 47/978 (5%) compared with 8/494 (2%) who received ivermectin. The decreases in blood pressure were transient, managed by resumption of recumbency and most commonly occurred on Days 1 and 2 post-treatment with moxidectin and slightly later post-treatment with ivermectin. Study participants should be advised that if they feel dizzy or light-headed after taking investigational product, they should lie down until the symptoms resolve.

Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision, photophobia, changes in visual acuity, hyperemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment without intervention.

Laboratory changes include eosinophilia, eosinopenia, lymphocytopenia, neutropenia, and increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH). Proteinuria has also been reported. These changes generally resolve without intervention.

10.5.1.2 Edema and Worsening of Onchodermatitis in Individuals with Hyperreactive Onchodermatitis (Sowda)

Moxidectin has not been evaluated in patients with hyper-reactive onchodermatitis (sowda), but based on the experience with other microfilaricidal drugs, such patients may be more likely than others to experience severe edema and worsening of onchodermatitis following the use of moxidectin tablets.

The same information is provided in the ivermectin Prescribing Information (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Symptomatic treatment has been used to manage patients who have experienced edema and worsening of onchodermatitis.

10.5.1.3 Encephalopathy in *Loa loa* Co-infected Individuals

Individuals heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma.

This syndrome has been seen very rarely following the use of ivermectin (ivermectin Prescribing Information,

https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Moxidectin has not been studied in individuals infected with *Loa loa*. Therefore, it is recommended that individuals who have had exposure to *Loa loa*-endemic areas undergo diagnostic screening for loiasis prior to treatment.

Consequently, the study areas selected for this study are not *Loa loa* co-endemic. Individuals with a history of living or working or still temporarily working in *Loa loa* endemic areas or symptoms suggestive of *Loa loa* infection such as eye worm will undergo screening for loiasis and, if found to be *Loa loa* infected, will be excluded from this study (Sections 7.3.1 and 7.4.7).

10.5.1.4 Comparative Data on Adverse Events after Moxidectin and Ivermectin Treatment

For comparative data on the incidence of AEs reported in the moxidectin and ivermectin treatment arms of the Phase II and Phase III studies, the Investigator is referred to the moxidectin Prescribing Information (available at Drugs@FDA; www.fda.gov/drugsatfda) or the Investigator's Brochure.

10.5.2 Risks during Pregnancy

The risks of treatment with moxidectin during pregnancy have not been evaluated.

There are no adequate and well-controlled studies of ivermectin in pregnant women and the US FDA approved prescribing information advises 'Ivermectin should not be used during pregnancy since safety in pregnancy has not been established' (https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf; http://edenbridgepharma.com/Ivermectin%20PI.pdf).

Therefore, pregnant women are excluded from the study and women of childbearing potential must commit to using a reliable method of birth control for the duration of treatment and until 3 months after completion of dosing. See Sections 6.4.1 and 7.4.5 for further details on pregnancy testing and contraceptive requirements.

10.6 Reporting of Pregnancies and Follow up of Pregnancies

The participants must be instructed to inform the Investigator immediately (women) if she becomes pregnant or (men) if his partner becomes pregnant during the study period.

The Investigator should report all pregnancies to the Sponsor Safety Desk (Section 10.3.3.1) within 24 hours of becoming aware of the pregnancy. Pregnancies, pregnancy outcomes and the findings should be reported using the appropriate form(s) for reporting the occurrence and outcome of pregnancies in participants having received a dose of investigational product in the study, or their partner.

Any participants (or their partner, if she agrees) who become pregnant within 3 months after administration of investigational product should be monitored until the end of the pregnancy. In addition, the outcome of the pregnancy should be followed for the first year of life and reported to the Sponsor.

The required information will be obtained from the local health clinics (see Section 5.2.3). The study team will advise women becoming pregnant up to 3 months after administration of investigational product to attend all ante-natal care visits, deliver at a health care facility and attend all post-natal care visits for the first year after birth provided by the local health care system. If necessary, the study team will facilitate attendance at these visits and delivery at the health care facility. The study team will collect the findings of the local health care

staff for reporting in the eCRF. The same applies for the partner of a male participant who becomes pregnant within 3 months of the male participant having received the investigational product, provided she agrees to her identity being provided to the study team and, if applicable, collection of the information from the health care clinics. In case of any abnormalities during the pregnancy or in the development of the baby during its first year of life for which a role of investigational product cannot be excluded, the team will arrange and pay for a specialist to evaluate the mother and/or the baby, as applicable.

10.7 Risks of Study Procedures Not Routinely Used in Health Care

10.7.1 Skin Snips

The only study procedure not used in routine health care is skin snipping.

Skin snipping is the gold standard for quantifying infection with *O. volvulus*. Skin snipping with microscopic determination of microfilariae in the snips was the standard method used by the Onchocerciasis Control Program in West Africa and APOC in collaboration with the National Onchocerciasis Control and Elimination Programs for assessing patent *O. volvulus* infection, including for assessing progress towards onchocerciasis elimination in DRC (Bas-Congo, Sankuru and Uélé), Congo (Bouenza, Pool), Burundi, Cameroon, Central African Republic, Chad, Ethiopia, Liberia, Malawi, Nigeria, Tanzania, and Uganda (Tekle et al. 2016).

Skin snip sites heal within four to eight days without intervention. Therefore, it is expected that most skin snip sites will be healed by the end of the five daily visits by a study team member after investigational product administration (Section 7.3.5). Should this not be the case, additional visits to the participant will be conducted as indicated.

Participants will be advised not to self-medicate but to contact a study team member or a local health facility should they need medical attention (Section 5.2.3 and 15.14).

10.7.2 DEC-Patch

DEC is microfilaricidal and causes a strong inflammatory reaction (Mazzotti reaction) around microfilariae. After application of a DEC containing patch, DEC penetrates the subcutaneous tissue underneath the patch. If microfilariae are present underneath the patch area, the inflammatory reaction results in a diagnostic skin reaction under the patch.

Another Mazzotti reaction *O. volvulus* infected individuals might experience after patch administration is itching around the patch area (Toe et al. 2000, Organisation mondiale de la Santé and Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest 2002, World Health Organization and Onchocerciasis Control Programme in West Africa 2002).

The clinical study comparing OCP-Patch and the DEC-Patch to be used in this study (Section 2.4.3) in 30 *O. volvulus* infected individuals showed that Mazzotti reactions other than the diagnostic skin reaction under the patch area (itching) were less frequent and of shorter duration after the DEC-Patch than the OCP-Patch (Awadzi et al. 2015) . Diawara and co-workers (Diawara et al. 2009) did not report any adverse events after application of the DEC-patch to 2283 people in whom no microfilariae were detected in the skin. However, an unspecified number of people had not returned for evaluation of the DEC-Patch reaction 24 hours after application.

Oral DEC was one of the drugs of choice for treatment and control of onchocerciasis. Its use was discontinued because Mazzotti reactions can be severe in highly infected individuals, including aggravation of ocular impairment, and blindness, and ivermectin became available as an effective and safe alternative.

Awadzi *et al* discussed in detail the probability of severe Mazzotti reactions in very highly infected people administered the DEC-Patch. They considered and compared

(a) the amount of DEC in the DEC-Patch (5.4 mg, manufacturing specifications range: 4.6 - 6.2 mg), the slow rate of penetration of DEC into skin (0.3 mg, 1.1 mg and 3 mg after 3, 8 and 24 hours), as well as the DEC half-life of around 9-10 hours, relative to doses used during oral treatment (single dose of 100 mg, total doses of 100 - 6000 mg, daily doses of e.g. 3 mg/kg/day for 7 days),
(b) the DEC dose-response curve for skin microfilariae density reductions relative to the maximum amount of systemically available DEC after DEC-Patch administration,
(c) the lack of impact of the DEC-Patch on skin microfilariae density around 1 cm away from the patch area, and
(d) the maximum number of microfilariae under the DEC-Patch area that could be killed in very highly infected people (2000 microfilariae/snip) compared with the maximum amount of microfilariae that would be killed after oral DEC treatment in people with low skin microfilariae densities (1 microfilaria/snip) in whom dangerous Mazzotti reactions have not been reported.

Based on these considerations and comparisons, severe Mazzotti reactions even in extremely highly infected people administered the DEC-Patch are very unlikely (Awadzi et al. 2015).

11 POTENTIAL BENEFITS TO STUDY PARTICIPANTS

Participation in the study is anticipated to provide a direct benefit to those with *O. volvulus* infection as all participants will receive an anti-onchocercal therapy. Based on data from the Phase III study, direct benefits anticipated include reduction in skin microfilariae density and, if applicable, in live microfilariae in the anterior chambers of the eyes. Reduction in microfilariae is a meaningful measure of treatment efficacy as clinical symptoms of onchocerciasis are caused by the hosts' inflammatory reactions to dying and dead microfilariae, including in the skin and eyes.

Participants excluded from the study because of a condition identified at Screening that requires medical attention will benefit from the Screening examination and receipt of referral information to a health facility.

Participants with a history of living or working or still temporarily working in areas where they might have become infected with *Loa loa* or signs and symptoms potentially caused by *Loa loa* infection, will benefit from having their *Loa loa* infection status evaluated. Those found to be *Loa loa*-infected will be given a note recording their infection status for presentation to the local onchocerciasis control/elimination (or lymphatic filariasis control/elimination) program and during ivermectin mass distribution so that the program can act accordingly (Section 6.4.2).

12 DATA SAFETY MONITORING BOARD REVIEW

A DSMB has been established by the Sponsor which is independent of the Sponsor, Investigators and site study teams. DSMB members were selected to include expertise in research methodology and statistics, pharmacology, clinical management and treatment of onchocerciasis, and pediatric and adult infectious diseases.

Meeting objectives and schedule are specified in a DSMB charter and span the requirements of this study, the study evaluating the safety and efficacy of annual and biannual treatments with moxidectin or ivermectin (Study 3001, conducted in Ituri, DRC), and the pediatric dose-finding study (Study 1006, conducted in Ghana). The DSMB may request additional review meetings.

Attendance at meetings will include DSMB members and non-voting members as required. Review of unblinded data may only occur in the presence of DSMB voting members and an unblinded biostatistician. Sponsor representatives may only attend that part of the meeting where data to be discussed remains blinded.

The first DSMB data review for this study will be convened after around 1000 participants have completed the 3 month follow up period.

The DSMB will review all SAEs reported during the first month after investigational product administration and provide a recommendation to the Sponsor on study continuation as planned, protocol amendment or study discontinuation, following which the Sponsor will determine study continuation, protocol amendment, or study discontinuation.

The outcome of the deliberations and recommendations of the DSMB to the Sponsor will be documented. The recommendations will be provided to the Investigator and the ECs.

13 PARTICIPANT COMPLETION OR WITHDRAWAL AND FOLLOW UP

13.1 Participant Completion

A participant will be deemed to have completed the study once all trial procedures have been conducted.

Any AEs or SAEs still ongoing at the End of Study Visit (Month 3, Section 7.3.6) or, for individuals withdrawing/withdrawn early, Exit Examination at Early Withdrawal or Early Study Termination (Section 7.3.7), will be followed in accordance with Section 10.4.

13.2 Premature Withdrawal from the Study

13.2.1 Criteria for Premature Withdrawal from the Study

Participants have the right to withdraw from the study at any time for any reason and without providing a reason. This will be discussed in the village meetings and with individuals (and their parents/guardians for minors) as per the information in the EC approved participant information document (Section 5.1 and Section 15.9).

The Investigator may also withdraw participants from the study in the event of concurrent illness or an AE if it is considered to be in the best interest of the participant.

The Sponsor and Investigator will discuss and agree whether withdrawal from the study may also be necessary in the case of protocol violations (e.g. continued failure or inability of the participant to be available for follow up visits).

13.2.2 Follow up of Participants Withdrawing or Withdrawn by the Investigator from the Study

Should a participant decide to withdraw from the study, all efforts should be made to contact them, determine the reason for the withdrawal (and resolve any misconceptions that might motivate participant withdrawal) if the participant is willing to provide it. Furthermore, the investigator should ask the participant for his/her agreement for an Exit Examination (Section 7.3.7) as close as possible to the planned 3 month follow up period as agreed by the former participant to monitor for possible investigational product related AEs.

The request to participants withdrawing from the study to agree to and Early Exit Examination (Section 7.3.7) is motivated by the following considerations: The Early Exit Examination is designed to characterize the health at the time of withdrawal. This is important independent of whether the participant withdraws because of an AE or for other reasons (including reasons they choose not to disclose). Participants withdrawing for AE-unrelated reasons may nevertheless have AEs that the investigator should identify for two reasons: (a) to offer the participant follow up of ongoing AEs and (b) to obtain as complete as possible characterization of the safety profile of the study drug.

Advice regarding participation in ivermectin distribution in the area will be provided. Furthermore, if permitted by the participant, follow up of AEs ongoing at the Exit Examination to resolution should be conducted.

As applicable, inability to reach the participant, reason for withdrawal (including unknown or unwillingness of the participant to provide it), refusal of the participant of the Exit Examination, or, if applicable, follow up of ongoing AEs or of a pregnancy, should be recorded in the source records and on the eCRF.

If the Investigator withdraws a participant from the study, the principal reason will be recorded in the source records and on the eCRF and the relevant activities specified above

for the case of a participant withdrawing implemented (provided the former participant agrees).

13.3 Replacement of Withdrawn Participants

Participants who decide to withdraw from this study or are withdrawn by the Investigator will not be replaced.

13.4 Temporary Suspension of Study Conduct

Continuation of the study and in particular, further treatment, may be temporarily suspended by the Sponsor, or on the recommendation of the Investigator or the DSMB based on identification of AEs that require further examination before continuation of the study. Study conduct will continue once the concerns that resulted in suspension have been addressed. The RAs and ECs will be informed about the suspension, its rationale and resolution of the concerns.

Continuation of the study may also be put on hold if requested by the RA or the responsible ECs, or the Sponsor (in response to information it generates/receives from sources outside of the study, including communications from the US FDA). Study conduct will continue once authorized by the RA, the responsible ECs, or the Sponsor, respectively.

13.5 Premature Termination of the Study

The study will be completed as planned unless the following criteria are met:

- New information regarding safety that indicates a change in the risk/benefit profile for moxidectin, such that this may no longer be acceptable to study participants, as per recommendation of the DSMB, the Sponsor (including in response to information it generates/receives from sources outside of the study, including communications from the US FDA), the Investigator, the RA and/or the responsible EC; and/or
- Significant violation of GCP that compromises the rights and safety of the study participants or the ability to achieve the primary study objective across all sites.

Sponsor and Investigators need to consult with each other before the decision to terminate the study prematurely and agree on a termination procedure to ensure that, for example, participant safety is protected (follow up of ongoing AE), investigational product is disposed in a manner consistent with the regulatory requirement and all study documentation stored in a manner that safeguards participant confidentiality.

13.6 Premature Termination of Study Conduct at a Particular Study Site

Conduct of the study may be terminated at a particular site if the Investigator or site staff are found in significant violation of contractual agreements or GCP or are unable to ensure adequate performance of the study.

Each Investigator has the right to request termination of the study at their site if the Investigator considers this to be in the best interest of current and potential future study participants' safety or finds it impossible to complete the study as required by the protocol and GCP. The Sponsor will notify the DSMB and other study Investigators in a timely manner regarding the request, to enable evaluation in the context of conduct at other sites and the study overall.

Sponsor and the relevant Investigator need to consult with each other before the decision to terminate the study conduct prematurely and agree on a termination procedure to ensure that, for example, participant safety is protected (follow up of ongoing AE), investigational product is disposed in a manner consistent with the regulatory requirement and all study documentation stored in a manner that safeguards participant confidentiality.

14 STATISTICAL ANALYSIS

This trial is a randomized, double blind, parallel group study comparing the safety of a single dose of moxidectin (8 mg) or ivermectin (approximately 150 µg/kg) for the control and elimination of onchocerciasis.

Following Baseline assessments, randomization and treatment, participants will be followed for 3 months.

For the purpose of the analysis, the term Baseline will refer to the last assessment taken prior to administration of investigational product and therefore includes assessments taken during Screening per the schedule in Table 1 if scheduled Day -1 to 0 (pre-dose) assessments are missing.

14.1 Primary Endpoint

The primary endpoint is the participant incidence rate of TEAEs, i.e. adverse events occurring, or worsening, after exposure to investigational product.

14.2 Sample Size

The sample size of approximately 12,500 and randomization ratio will provide safety data for up to approximately 10,000 exposures to moxidectin and 2,500 exposures to ivermectin, providing a probability of around 0.99 and 0.71 to detect at least 1 AE with a true background rate of 5/10000, respectively assuming exposures are independent.

14.3 Randomization and Randomization Ratio

Participants will be randomized in a ratio of 4:1 to moxidectin and ivermectin, stratified by Screening skin microfilariae density (Section 8.1).

The 4:1 randomization ratio for the moxidectin and ivermectin treatment arms was chosen to maximize the safety data base after exposure to moxidectin while preserving the ability to compare the type, frequency and severity of AEs after moxidectin with those after ivermectin in the same population within the same time period.

Each site will have its own set of randomization lists. Depending on the size of the geographic area over which a particular site will be recruiting participants, additional stratification by an appropriate geographic area defining criterion may be introduced for that site. The randomization lists will be generated by an independent statistician not otherwise participating in the study. The randomization algorithm implemented will be documented, remain secured by the independent statistician, and provided in the clinical study report.

14.4 Analysis Population

The safety analysis set is defined as all randomized participants exposed to investigational product and will be the only analysis population. Participants will be analyzed according to the actual investigational product received regardless of their randomized treatment group.

14.5 Group Comparability

Since the study is randomized it is expected that the treatment groups will be balanced with respect to known and unknown prognostic factors.

Exploratory subgroup analyses and/or statistical models adjusting for baseline covariates known or suspected as being prognostic factors, other than those pre-specified, may be conducted for descriptive and supportive purposes.

14.6 Data Analysis Methods

Aggregate data summaries will be provided by treatment group overall, by site and by Screening skin microfilariae densities and overall. Data summaries will also be provided as relevant by study time point. Line listings of study data will also be included.

Unless otherwise stated, all p-values will be two-tailed. Adjustment for multiple comparisons will not be conducted.

Further analysis details will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to unblinding and the undertaking of any analysis. Any changes to the finalized SAP will be documented. Deviations from the planned statistical analyses outlined in the SAP will be identified and described in the clinical study report.

14.7 Statistical and Analytical Plan

14.7.1 Statistical Analysis of the Primary Endpoint

Participant incidence of TEAEs will be summarized by body system and preferred term overall, and by site.

TEAEs will be tabulated by severity, physician assessment of relationship to investigational product, serious TEAEs and TEAEs leading to death or study withdrawal, overall and by site.

Key TEAEs of interest may be further analyzed via the calculation of 95% CI for subject incidence rates and/or using Kaplan-Meier methods to assess time-to-first events and/or time-to -resolution. Additionally, for key TEAEs exposure adjusted rates may be provided.

TEAE will also be summarized by participant age and by sex and by screening skin microfilariae density.

Line listings of all TEAEs will be provided.

14.7.2 Analysis of Participant Disposition, Demographics, and Baseline Skin Microfilariae Density

Descriptive summary tables will be provided across the whole study and by site summarizing participant disposition by treatment received, including all participants randomized regardless of exposure to investigational product along with reasons for early withdrawal from the study.

Demographic and medical history summary statistics will also be provided overall and by site by treatment and overall.

14.7.3 Analysis of Other Safety Related Data

Other safety relevant data analyzed will include concomitant medication for TEAEs and pregnancy outcomes. Adverse events before investigational product exposure will be listed.

14.7.4 Handling of Missing Data

Other than for partial start/end dates for AE and concomitant medications, no imputation will be made. Imputation of partial AE and concomitant medication dates will be done to categorize an AE or medication as having started or been taken before or after the treatment, respectively. Details of the imputation algorithms will be provided in the SAP.

14.7.5 Interim Analysis

A DSMB will review safety data for the duration of the study (Section 12).

No interim analyses are expected to be conducted.

14.7.6 Supplemental Analyses for Informing Guidelines and Policies

14.7.6.1 Analyses of the Safety of Moxidectin and Ivermectin

The types of analyses required by regulatory agencies do not always meet the requirements for decisions on inclusion of an intervention in guidelines and policies. A separate SAP will be written for supplemental analyses addressing these requirements. These analyses will not be executed until the Study's conclusion.

14.7.6.2 Evaluation of the DEC-Patch during Screening

The analysis population for the add-on evaluation will include all individuals to whom the DEC-Patch was applied.

The proportion of individuals will be summarized by presence and by extent of skin reaction (scores) under the DEC patch overall and by presence of microfilariae and microfilariae densities.

Participant incidence of AEs starting after application of the DEC-Patch and recorded at the time of removal of the patch will be summarized by body system and preferred term and by presence of microfilariae and microfilariae densities.

Further details will be provided in a specific SAP. Since the relevant data are obtained before investigational product administration and their analysis does not require unblinding, the analysis may be conducted before completion and unblinding of the study.

14.7.7 Update of Statistical Analysis Plans in View of Potential Impact of COVID-19 Pandemic on Study Conduct and Data

Before unblinding, the data will be reviewed to assess which protocol deviations such as treatments or safety assessments that were missed or conducted outside the protocol prescribed window are attributable to the COVID-19 pandemic. The Statistical Analysis Plans will then be updated to reflect complementary or appropriately modified approaches to the analyses.

15 ETHICAL ASPECTS

15.1 Declaration of Helsinki and Applicable Regulations

The Investigator will ensure that this study is conducted in full conformance with the protocol, the latest version of the Declaration of Helsinki, the International Ethical Guidelines for Health-related Research Involving Humans of the Council of International Organizations of Medical Sciences (CIOMS), the ICH-GCP Guideline and all applicable regulations.

15.2 Approval of Study Conduct by the Regulatory Authorities

This protocol, material used to inform potential study participants about the study (PICFs), the Investigator's Brochure and a dossier on the investigational medicinal products will be submitted by the Sponsor through the Investigator to the RA. Approval of study conduct by the RA is required before the study can be started.

Protocol amendments as well as memoranda summarizing administrative changes of the protocol (Section 15.5) will be submitted to the RA as specified in the letter of approval of study conduct.

15.3 Ethics Committee Approval

This protocol, PICFs and the Investigator's Brochure, will be submitted to the relevant EC. Furthermore, they will be submitted to the WHO Ethics Review Committee.

Approval from the ECs must be obtained before starting the study, specifying the protocol number and/or title and protocol version, PICF version number and/or date and the date on which the EC met and the date the EC granted the approval and/or the date of signature on the approval.

Any protocol amendments (Section 15.5) after receipt of the original EC approval must also be submitted to the EC and approved by the ECs before the amendment can be implemented (except where required to ensure participant safety). The ECs will be notified of changes to the protocol that are purely administrative (Section 15.5).

Documents to be used for informing participants of any early termination of the study (Sections 13.5 and 13.6), new data that might impact their decision on continued study participation (Section 15.10) and the results of the study (Section 15.23) will also be submitted for EC approval prior to use.

15.4 Reports to RAs and ECs

Reports to the RAs and the ECs will be submitted as requested by the RAs and ECs in their decision/approval letters. In the absence of specific requests, a progress report summarizing the number of individuals screened and treated in the past year and the number and type of SAEs reported since the last report will be submitted to the ECs annually.

15.5 Protocol Amendments

Administrative changes of the protocol are defined as corrections and/or clarifications that have no effect on the safety of the participant, scope, design, assessments or scientific validity of the study. These administrative changes will be agreed upon by the Sponsor and the Investigator and will be documented in a memorandum. The Investigator will then notify the EC and the RA of these administrative changes.

Other modifications of the protocol (protocol amendments) must be prepared in consultation between the Sponsor and the Investigator and must be reviewed and approved by the Sponsor-designated Medical Monitor and the Statistician before signing off by the Sponsor

and the Investigator. Investigator and Sponsor-approved protocol amendments will be submitted to the RAs and ECs. They must be approved by the RA (if indicated in the RA study approval letter) and/or ECs prior to the amendment being implemented.

In the event of an emergency, the Investigator may institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor Clinical Development Manager for this study and the Medical Monitor, and the ECs.

15.6 Study Site Capacity

Details are provided in Attachment: Country-specific Information.

15.7 Study Team

Details are provided in Attachment: Country-specific Information.

15.8 Study Initiation

The study can only be started after approval by the RA and ECs and after the Sponsor has approved study start following the study initiation visit.

The objective of the initiation visit is to verify that the Investigator and study team have the means and knowledge to conduct the study. During the initiation visit, the Sponsor representative(s) will review with the Investigator and study team all Declaration of Helsinki, CIOMS and ICH-GCP requirements, the profile of AEs occurring after ivermectin and moxidectin treatment, all protocol requirements, study required equipment, material and consumables, study implementation plans including plans for study participant recruitment, SOPs, study documentation requirements including source records, eCRFs (Section 16) and SAE reporting requirements and forms (Section 10.3.3), pregnancy reporting and follow up requirements and forms (Section 10.6) study team training records and the study Authorization and Delegation Log. This verification review will include the review of study team member CVs and copies of qualification or licensure documents to confirm that study team members have the qualifications the law of the country where the study is conducted requires for the activities delegated to them on the study Authorization and Delegation Log, as well as records of training on study procedures delegated to them and which are not part of routine health care (e.g. skin snipping, counting of microfilariae).

Furthermore, team members will be trained on the use of the eCRF and data management processes (Section 16.2). The Sponsor will ensure that its representatives are fluent in both English and French if the country is francophone.

Any deficiencies found will be discussed with the Investigator and need to be addressed before the Sponsor will approve study start.

15.9 Informed Consent and Assent with Parental/Guardian Consent

It is the responsibility of the Investigator to obtain written informed consent (or informed assent from minors with parental/guardian informed consent) from each individual participating in this study after explanation of the aims, methods, objectives and anticipated benefits and risks of the study in the local language (see Attachment: Country-specific Information) and wording they can understand. The Investigator must also explain to the potential study participants that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The Investigator must utilize the EC-approved PICF for informing potential study participants and for documenting written informed consent/assent.

Information about the study will be provided and written informed consent or assent with parental/guardian consent obtained by a physician. Should the physician not speak the local language, another member of the study team who speaks the local language must be present to act as interpreter. The study team members authorized to inform study participants of the study and obtain written informed consent/assent with parental/guardian consent will be documented on the Authorization and Delegation Log.

The appropriate consent or assent with parental/guardian consent must be obtained before any Screening or other study procedures are initiated (Section 6.1).

The information and consent/assent forms in the protocol language and the local language(s) of the planned study populations (see Attachment: Country-specific Information) will be included separately in the RA and EC submissions. A final approved version of these documents will be retained in the study files and must be used in the informed consent/assent discussions with potential study participants.

15.9.1 Considerations during the Development of the Participant Information Documents

The Participant Information documents were written, and the wording chosen to fit:

- The planned step-wise process (Section 5.5.2) for informing communities and interested individuals about all aspects of the study required for the community to advise on study implementation and for individuals to decide upon their own or their child/ward's participation;
- The full age range for study eligibility so that adolescents and their parents/guardian can be informed simultaneously;
- The notions in the population in the recruitment areas to ensure that they are familiar with specific concepts presented or that these concepts are explained or presented in terms meaningful to the potential participants (for details see Attachment: Country-specific Information.

15.9.2 Provisions for Informed Consent and Assent with Parental/Guardian Consent by Illiterate Individuals

A high percentage of the population in the recruitment areas is illiterate (see Attachment: Country-specific Information). Furthermore, the 'literacy' criteria from the Informed Consent/Assent perspective are much higher than the criteria used locally. To avoid that these different literacy criteria and different provisions for informed consent/assent from illiterate and literate individuals are perceived as insulting or lack of respect, it was decided that a literate witness will be required for all participants.

Consequently, all adults and minors will confirm their consent or assent with parental/guardian consent via signature, mark or finger print (as per their preference) on the consent form in the presence of a literate witness they have chosen. The literate witness will confirm through their dated signature that they were present when the information was provided and that they witnessed that any questions asked were answered to the satisfaction of the potential participant and their parent/guardian, if applicable, and that voluntary informed consent or assent with parental/guardian consent was given.

15.9.3 Provisions for Informed Assent for Minors with Parental/Guardian Informed Consent

Informed assent with written parental/guardian consent will be obtained for minors aged 12 to 17 years old.

Refusal of the parent(s)/guardian or minor constitutes dissent and precludes the minor's participation in the research. Every effort should be made to obtain, if possible, the consent of both parents.

In order to respect local culture and unless otherwise advised by the RA or the ECs, for orphans living with relatives, the head of the household (guardian) will be providing informed consent to complement the minors informed assent as the guardian.

Minors living with family members other than their parents, will require parental consent.

If an adolescent turns 18 years old during their participation in the study and is no longer a minor, he or she will be asked to provide written informed consent as soon as practically reasonable on the same form the minor signed for assent.

15.10 Information to Study Participants in Case of New Data Emerging During the Course of Their Study Participation

Should new data emerge during the course of this study that may affect the willingness of study participants to continue in the study, the data will be submitted to the ECs together with a PICF for informing the study participants about these data as a basis for their decision to continue study participation.

Upon approval of the PICF by the ECs, study participants will be contacted to provide and discuss with them this information and ask them about their decision or not to reconsent (or re-assent with parental/guardian re-consent). The Investigator will seek guidance from the chiefs and elders of the villages where the participants live on how to provide the information (e.g. participant meeting, visit to each individual participant).

At the time these data emerge, the PICFs for use during continued recruitment of new participants will be updated accordingly and submitted to the EC for approval.

15.11 Information to Study Participants about 'Incidental Findings'

Health problems identified during Screening or a study that are not related to the health problem being studied (in this case onchocerciasis and the response to the administration of moxidectin or ivermectin) are these days sometimes referred to as 'incidental findings'. Plans for informing participants need to distinguish 'anticipatable' findings (i.e. health problems known to be diagnosed with the examinations and tests used) and 'unanticipatable' findings (i.e. health problems that cannot be expected to be identified based on current state of scientific knowledge).

All examinations and tests used in this study are long established and not undergoing further scientific/methodological development (in contrast to, for example, imaging methods). Consequently, all health problems identified at each visit are 'anticipatable'. All of them will be discussed with the participant and treatment will either be provided by the study team or the participant will be referred to the health system for appropriate care.

'Unanticipatable' findings could only emerge from the use of the *O. volvulus* microfilariae or left over urine during research for improved tools and strategies for control and elimination of onchocerciasis and other Neglected Tropical Diseases (Sections 15.19, 15.20). The Sponsor has developed a process that provides for the scientists who conduct the research on the left-over *O. volvulus* parasites and left over urine to report any findings that they consider of possible interest for the health of a participant to the Sponsor. The Sponsor will convene a meeting of members of the DSMB, clinicians specializing in the discipline(s) indicated by the nature of the unanticipated finding and the Investigator (or delegate) to discuss the possible clinical significance of the unanticipated finding. This process also ensures that the participant anonymity will be preserved. Unanticipated findings will be

provided to the participant only if approved by the EC of the country where the participant lives based on a dossier submitted that details the unanticipatable finding, the process and outcome for validating its health significance and the actions that can be taken for the benefit of the participant. In the Participant Information document, potential participants are told that it is unlikely that the research on their *O. volvulus* parasites or left over urine will reveal any information relevant for their health, but that if this is the case, they will be informed.

15.12 Risks due to Study Procedures

Information on risks associated with study procedures which are not used during routine health care is provided in Section 10.7.

15.13 Risks Associated with Investigational Products

Information on risks associated with moxidectin and ivermectin are provided in Section 10.5.

15.14 Compensation of Study Participants for Time Spent on the Study and Costs Incurred for Treatment of an AE in a Local Health Facility

As study participants will be recruited among villagers who are continuing to pursue their usual daily activities, the time participants spend on study activities will be time they are unable to pursue gainful work. To compensate study participants for the resulting loss of earnings, participants will be compensated for time spent undergoing study assessments with the average daily earning of the population from which the study participants are being recruited (see Attachment: Country-specific Information). The time spent prior to Screening (i.e. for informing the potential participants and obtaining informed consent to Screening) will not be compensated for.

On Day 1 to Day 5 after investigational product administration, when the reactions to the microfilaricidal effect of moxidectin or ivermectin typically start and resolve (Section 10.5), an appropriately trained study team member will visit each participant daily (Section 7.3.5). If after that period study participants chose to visit a local health facility rather than contact the study team (directly or via the SFP, (Section 5.2.4)) because of an AE, study participants will be compensated for any costs incurred for visiting the local health facility and for the treatment of an AE in the facility if that AE could possibly, probably or definitely be related to treatment with ivermectin or moxidectin.

Study participants will not be compensated for costs incurred for treatment at health facilities of AEs unambiguously not related to investigational product or study conduct (e.g. malaria, appendicitis, snake bites, respiratory infections, intestinal infections and parasitosis, epilepsy, trauma) or treatments they obtained from traditional healers.

15.15 Safety of Study Participants Withdrawing Prematurely from the Study

For provisions to ensure follow up of study participants withdrawing or withdrawn from the study, see Section 13.2.

15.16 Volume of Blood Sampled

Blood (0.06 ml) will be drawn only in case infection with *Loa loa* (0.06 ml) is suspected (Section 6.4.2 and Section 7.4.7).

15.17 Confidentiality of Trial Documents and Participant Records

The Investigator must ensure that the participants' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents

submitted to the Sponsor, participants will not be identified by their names, but by the code assigned to each participant (Section 7.4).

The Investigator will keep a participant screening log showing the names and addresses as well as participant codes. This log, as well as other documents not for submission to the Sponsor (e.g. participant's signed informed consent/assent forms), will be maintained by the Investigator in strict confidence.

All documents with results of the examinations conducted during this study, including, but not limited to the documents identifying study participants by name, will be stored in a locked cabinet or room with access restricted to authorized study team members and electronic records will be password protected (Sections 16.1 and 16.2).

15.18 Clinical Trial Insurance

Clinical trial insurance equivalent to at least US$10,000,000 has been secured by the Sponsor to provide appropriate compensation to the participants should they suffer harm as a result of their participation in this study, including the add-on evaluation of the DEC patch. This will also provide financial protection for those responsible for review and approval of the study protocol and for its conduct.

An insurance form and policy will be provided to the RAs and ECs as required at the time of protocol submission.

15.19 Ownership and Future Use of Biological Specimen Remaining After Completion of the Protocol Required Examinations

Biological specimens (*O. volvulus* microfilariae, urine) will be owned jointly by the Investigator's organization (see Attachment: Country-specific Information) and the Sponsor who agree to make these available for other research, in the interest of developing new tools and strategies primarily for onchocerciasis and secondarily for other NTDs prevalent in Africa.

This intended use and the duration of the sample storage (20 years) is included in the PICF for potential participants.

Should specimens be requested by for-profit organizations, the Investigator's organization and the Sponsor will negotiate with the potential specimen users provisions for access to resulting products for the public health systems in the African countries at cost, with no more than a minimum profit margin. A dossier summarizing the intended use and commitments of potential for-profit users will be submitted to the EC and the RA of the country where the biological specimen were obtained for approval before specimens are provided.

In all cases, specimen-accompanying information collected during this study needed for the research will be anonymized and the transfer covered by a Material Transfer Agreement. The Material Transfer Agreement will also specify that the researchers have to inform the Sponsor should they identify 'unanticipatable findings' (Section 15.11).

For further information on identified recipients of the parasites and left-over urine see Section 15.20.

15.20 Maximization of Study Outputs for Improved Tools and Strategies for Control/Elimination of Onchocerciasis and other Neglected Tropical Diseases

15.20.1 Use of Skin Microfilariae

The challenges African onchocerciasis endemic countries face for elimination of onchocerciasis transmission include that onchocerciasis is endemic across large contiguous areas which cross administrative boundaries within countries and borders between countries. Furthermore, different areas and countries initiated mass drug administration at different times and implementation has encountered different challenges. This is particularly so for countries suffering from past or current conflict, such as DRC. It results in different areas reaching the criteria for stopping treatment at different times. The recent WHO 'Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis' provide criteria for when transmission can be considered interrupted within a transmission zone so that mass drug administration can be stopped, but does not provide criteria for delineating transmission zones (World Health Organization 2016).

To ensure that treatment is stopped in one area only when stopping criteria are met across the total geographic area of a 'transmission zone', and to minimize the risk that new infections are introduced from neighboring areas where transmission is still ongoing into areas where mass drug administration was stopped, countries need tools to delineate transmission zones.

Research for such a tool is currently ongoing through WHO /TDR (Hedtke et al. 2020). The research also targets a tool to allow control/elimination program to quantify the number of reproductively active male and female *O. volvulus* that contributed to a sample of parasites obtained from skin snips or infected/infective vectors and to monitor the prevalence of suboptimal response to ivermectin. One of the WHO/TDR funded investigators (Dr. W. Grant) at La Trobe University, Melbourne, Australia, has received a grant from United States of America National Institute of Health which allows to significantly accelerate progress towards the WHO/TDR targeted tools and includes funding for the preservation and shipment of parasites for this research. Following completion of skin microfilariae counts, the microfilariae will be preserved in alcohol and shipped to Dr. Grant (Section 7.4.6). Samples will be anonymized and shipped under a Material Transfer Agreement which specifies 20 year maximum storage time and that all parasite sequences obtained during this research will be deposited in a publicly available repository.

Parasites not needed for this research will be shipped anonymized and under a Material Transfer Agreement to the ‘Molecular Resources Division’ of the NIH-NIAID Filariasis Research Reagent Resource Center (FRRRC, or FR3, http://www.filariasiscenter.org/, http://www.filariasiscenter.org/resources/molecular-resources) to ensure that they can be used world-wide for research in support of control and elimination of NTDs.

FR3 was established in 1969 and has a long history of partnership with (and at times funding from) WHO and supporting WHO funded researchers (including WHO/TDR funded research which led to development of moxidectin for onchocerciasis) (Michalski et al. 2011). FR3 not only provides material to researchers world-wide but also offers free protocols and technical support to researchers. Over the past 7 years, FR3 has made 741 shipments to recipients in 61 countries, including 33 countries in Africa (Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Democratic Republic of the Congo, Ethiopia, Gabon, Gambia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Namibia, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, South Africa, South Sudan, Sri Lanka, Swaziland, Tanzania, Togo, Uganda)

(personal communication to Annette C. Kuesel, WHO/TDR, by Dr. Steven A. Williams, Director of Molecular Resources FRRRC, Director of the River Blindness Genome Project, Coordinator of the World Health Organization Filarial Genome Project, http://www.filariasiscenter.org/resources/molecular-resources). Prerequisite for receipt of material by researchers is signature of a Material Transfer Agreement customized by the owner of the samples, i.e. those providing the material to FR3.

15.20.2 Use of Left-over Urine

For provisions for preservation of urine left over from pregnancy tests and future use for research, see Attachment: Country-specific Information.

15.21 Complaints Process

During the consultation with village communities during study preparation (Section 5.1), paths for study participants to convey complaints or suggestions to the study team will be discussed. Independent of whether they choose to provide these via intermediates (e.g. village chief, SFP) or directly to a study team member, feedback will be provided by a study team member. The study team member providing the feedback will be selected by the Investigator depending on the type of feedback/complaint.

15.22 Ownership of Study Data

The data generated during the study will be owned by MDGH as per the agreement for the EDCTP grant concluded by MDGH and the institution of the principal investigator. MDGH has committed to providing anonymized study data to the US FDA in support of a request to expand the moxidectin US Prescribing Information (see Section 18).

In addition, MDGH will provide the anonymized data and reports to the WHO and country policy makers at their request.

15.23 Post-Study Activities

15.23.1 Post-Study Reports to RA and EC

Following completion of the data analysis, a summary report will be provided to the RA and the ECs.

15.23.2 Post-Study Information about the Study to Study Participants

The summary report to the ECs will be accompanied by an Information Document containing the information to be conveyed to study participants about the results of the study and planned future activities. This EC-approved Information Document will be the basis for informing the study participants (and interested other inhabitants of their villages) about the study.

At that time, participants will also be informed about whether they received moxidectin or ivermectin.

15.23.3 Post-Study Reports to Other Stakeholders

Summary reports will be provided to and discussed with other relevant stakeholders, including those involved in the preparation of this study (Section 5.1) and presented to the Onchocerciasis Control and Elimination Programmes of the countries where this study is conducted, WHO/AFRO Expanded Special Project for Elimination of Neglected Tropical Diseases and relevant departments in WHO Headquarters.

15.24 Post-Study Access to Moxidectin

Moxidectin has been approved in the US for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older, but is not yet registered in any other countries. Consequently, moxidectin cannot be provided post-study to the population in the study areas or anywhere else without approval by the RA via registration of moxidectin in that country, another type of authorization, or during a RA and EC approved clinical trial.

At the request of the RA, the Sponsor will submit the dossier that formed the basis of the US FDA registration to the RA.

Given that the dossier is in English and includes >400 000 pages, the Sponsor is exploring the possibility for registration via the 'Collaborative Procedure for Accelerated Registration' of drugs approved by stringent regulatory authorities such as the US FDA currently being piloted by WHO with primarily African countries (https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras (World Health Organization 2018).

Until moxidectin has been integrated into WHO guidelines and/or onchocerciasis control/elimination policies in the countries where this study is being conducted, the Sponsor will ensure access to treatment with moxidectin to clinical trial participants and their communities, provided the Sponsor receives the appropriate request with authorization and implementation and pharmacovigilance plans from the Ministry of Health/RA.

15.25 Provisions for the implementation of the Study during the COVID-19 Pandemic

All activities required for successful implementation of the study, ranging from community mobilization and information (Section 5), over obtaining informed consent/assent (Section 15.19) to screening, treatment and follow up (Sections 7.3 and 7.4) were reviewed in conjunction with the relevant national and local guidance on management of the COVID-19 pandemic.

The objective of this review was to determine whether the study can be conducted during the pandemic in a way that minimizes risk of transmission of SARS-CoV-2 and could have an overall positive benefit-risk ratio through re-enforcement of the education of the population in the villages in the recruitment area on COVID-19 measures and contribution to screening for COVID-19 cases.

Specifically, the review of the activities determined:

- the extent to which they can be conducted with physical distancing and the operational measures to be taken,
- the extent to which those involved will have already undergone education on COVID-19 and required pre-cautions to minimize SARS-CoV-2 transmission,
- the need for the study team to provide the initial education on COVID-19 (based on Information, Education and Communication material provided by the local COVID-19 task force) vs. re-enforcing previous education about COVID-19 provided by the local COVID-19 task force,
- how screening for suspected COVID-19 cases through temperature measurement, questioning for symptoms defining individuals as suspected COVID-19 cases, advice to such cases to self-isolate and information to the responsible public health system units can be incorporated and take place at the beginning of all other protocol planned activities,
- additional measures that need to be taken to minimize the risk of SARS-CoV-2 transmission during all activities where physical distancing is not possible.

The details of the measures to be taken during the different activities are provided in Attachment: Country-specific Information. As national or local health system directives evolve during the course of the pandemic, the measures described in the Appendix will be adapted accordingly.

Furthermore, in view of possible outbreaks of potentially life threatening diseases (such as Ebola or COVID-19), treatment with investigational drugs or vaccines for such diseases have been included among permitted investigational products in Section 9.3.

All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the national/local COVID-19 response team which will also ensure that the study will adapt its measures as required by changing government/health system guidance. All communication and community engagement about COVID-19 will be done in coordination and collaboration with the national/local COVID-19 response team and based on their communication material.

16 STUDY DOCUMENTATION, eCRFs AND RECORD KEEPING

16.1 Source records

Data collection is the responsibility of the clinical trial site staff, under the supervision of the site Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility and veracity of the reported data.

The data will be documented either on paper (written records, print outs of analytical devices) or onto a tablet equipped with the CliniOps App Suite developed by CliniOps (a Mobile, Cloud-based, Digital Solutions company based in Freemont, CA, USA) that allows storage and backup of all data entered as well as uploading of selected data into the eCRF. Data documented with this Direct Data Capture system are referred to as electronic source data (eSource).

All paper source records should be typed or filled out using a black or blue pen and must be legible. Errors should be crossed out with a single strike line and not obliterated (e.g. via use of correction fluid), the correction inserted, and the change initialed and dated by the Investigator or his/her authorized delegate. Printouts and photos that might fade overtime should be copied and/or digitized to ensure long-term availability.

The data to be captured manually or as eSource will be agreed between the study team and the Sponsor and documented prior to initiation of the study.

16.2 Electronic Case Report Forms and Data Management

For each participant screened, an eCRF must be completed and signed electronically by the Principal Investigator or delegated co-Investigator. For requirements for eCRFs for participants who withdraw from treatment or from the study or are withdrawn from treatment or the study by the Investigator, see Section 13.

In view of the possible impact of the COVID-19 pandemic on study conduct, the eCRF will include fields allowing to capture which protocol deviations are attributable to the COVID-19 pandemic (including, but not limited to, study participants cannot be treated or assessed within the protocol specified time frame because they are self-isolating, or they or their family are under quarantine, or study team members are under quarantine).

The eCRF software developed by CliniOps is compliant with the US Code of Federal Regulations for Electronic Records and Electronic Signatures (21 CFR Part 11) and the US Health Insurance Portability and Accountability Act (HIPAA) and is validated to meet data security, data quality and data monitoring requirements in accordance with ICH GCP guidelines. The data system includes password protection and internal quality controls, such as automatic range checks, to identify data that appears inconsistent, incomplete or inaccurate.

Participants will be identified in the eCRF only via their participant code, not by name or any other information that might allow to identify the participant (see Section 15.17).

Data management will be conducted by Sponsor-trained study team members at the site and by CliniOps, contracted by the Sponsor. The data manager at CliniOps will implement integrated testing and verification controls to ensure data completeness and internal consistency. Each operation performed is tracked by an audit trail. Each person at CliniOps is subject to professional secrecy.

16.3 Investigator’s Files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These

documents should be classified into two separate categories: (i) Investigator's Study File, and (ii) participant source records.

The Investigator's Study File will contain essential documents such as the protocol/amendments, EC and RA approvals with correspondence, approved PICF and signed consent/assent forms, screening logs, randomization lists, investigational product records, staff curricula vitae and authorization forms and other documents and correspondence. The eCRFs with data queries and audit trails will also be retained in an archive acceptable format.

Participant source records may include physician's and nurse's notes, original laboratory reports, and any other records generated during and for this study.

The storage system used during the trial and for archiving (irrespective of the type of media used) will allow for document identification, version history, search, and retrieval. The Sponsor will ensure that the Investigator has control of and continuous access to the data reported to the Sponsor. The Investigator will have control of all essential documents and records generated by the investigator and the study team before, during, and after the trial.

All essential documents should be retained for at least 25 years after the end of the clinical trial. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the investigator/institution as to when these documents no longer need to be retained. The Investigator must notify the Sponsor prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party (due to retirement or leaving the site organization) or to move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where eSource/source records are required for the continued care of the participant, appropriate copies should be made, or extracted from the Direct Data Capture system in the case of eSource, as applicable, for storage outside of the site.

17 MONITORING, AUDITING AND INSPECTION OF THE STUDY

17.1 Access to Source Records

The Investigator shall supply the Sponsor, on request, with any required study documentation and records generated during examination of participants or analysis of the biological samples obtained during the study. This is particularly important for source data verification or when errors in data transcription are suspected.

In case of governmental or regulatory queries or requests for audits and inspections, it is also necessary to have access to the complete study records. Individuals authorized by governmental and regulatory agencies to audit or inspect studies have the obligation to respect participant confidentiality.

17.2 Monitoring of the Study

The study will be monitored by an unblinded monitor to review randomization and investigational product dispensing and a blinded monitor to review all other activities. Monitoring will occur by on-site visits and/or remotely at a frequency specified in the Monitoring Plan or more frequently, if triggered by observations made during a visit, remote monitoring or as requested by the DSMB.

It is understood that the responsible monitors, as a Sponsor representative, will be fluent in English and the language spoken by the Study Team members and contact and visit the Investigator in person or electronically regularly and that he/she will be allowed, on request, direct access to the source records as per ICH-GCP guidelines to inspect the various records of the trial (eCRFs, signed consent/assent forms, laboratory test reports, participant records in local health facilities the study participant might contact and other pertinent data, randomization and investigational product dispensation records) provided that participant confidentiality is maintained as required by ICH-GCP.

It will be the monitor's responsibility to inspect such documents, to verify the adherence of study conduct to ICH-GCP requirements and the protocol and to verify the completeness, consistency and accuracy of the data entered on the eCRF.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17.3 Audits and Inspections

The Investigator/Institution will also permit trial-related audits, EC review, and regulatory inspection(s), providing direct access to source records to appropriately qualified personnel from the Sponsor or its representative who speak English and the language of the study team, or to RA or health authority inspectors or EC representatives after appropriate notification. The verification of the eCRF data may be by direct inspection of source records (where permitted by law) or through an interview technique.

Sponsor quality assurance audit(s) may be conducted during the study and/or preceding a planned regulatory inspection.

Inspections by RA are at their discretion and cannot be foreseen. It is usual practice for regulatory authorities of foreign countries (e.g. US FDA or the regulatory authorities of other countries considering approval of moxidectin) to contact their counterparts in the RA of the country where the study is conducted when considering an inspection.

18 CONDUCT OF THE STUDY IN VIEW OF MDGH'S US FDA INVESTIGATIONAL NEW DRUG APPLICATION

MDGH opened US FDA IND application 126876 as part of MDGH's interactions with the US FDA which resulted in the 2018 US marketing approval of moxidectin for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older (US FDA NDA 210867).

This study will not be conducted under this IND, but as a 'foreign study'.

18.1 Reporting to US FDA During the Study

As required under the IND, MDGH will provide annual safety updates on this study to the US FDA.

18.2 Reporting to US FDA After the Study

Upon completion of this study, MDGH intends to submit the final clinical study report to the US FDA in support of a request to update the moxidectin US Prescribing Information with comparative data on the safety of moxidectin and ivermectin. If approved, this will provide a US Prescribing Information for moxidectin that is more closely aligned with the anticipated use of moxidectin in the field.

19 PUBLICATIONS

MDGH will also update the study entry on www.ClinicalTrials.gov with significant study status updates and to include a summary of the study results when available, which will not contain information that could identify participants.

The Sponsor has also listed the study on the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/).

Once approved by the RA and the ECs in one country, the protocol will be made publicly available.

The results of this study will be published in peer-reviewed open access journals and presented at scientific meetings. Sponsor-initiated publications and/or presentations will be agreed upon between the Investigators and Sponsor. Publications reporting analysis of the data acquired at an individual site should be preceded by the publication of the data from all sites analyzed as per the statistical analyses planned in this protocol. Investigator-initiated publications and/or presentations will be provided for review by the Sponsor at least 30 days before the submission deadline for the manuscript and/or presentation abstract to enable relevant input based on information from other studies that may not yet be available to the Investigator.

Any formal publication of the study in which input of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel. Authorship will be determined by mutual agreement in accordance with International Committee of Medical Journal Editors recommendations. Additional authors will be agreed prior to journal submission.

Oral or written presentations or publications will mention "this research is part of the EDCTP2 Programme supported by the European Union (grant NUMBER RIA2017NCT-1843)".

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21 APPENDICES

21.1 Appendix 1: Adverse Events Toxicity Grading Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Major Clinical Conditions: Cardiovascular				
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities [1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
Dermatologic				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA

[2] As per Bazett's formula.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] [3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Endocrine and Metabolic				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic interventio n indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Interventio n indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6][6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Neurologic				
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if* *applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
Pregnancy, Puerperium, and Perinatal				
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID)	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Report only one				
Psychiatric				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted
Respiratory				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
		Pulse oximetry 90 to < 95%		
Sensory				
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech- language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
Systemic				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Urinary				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Site Reactions to Injections and Infusions				
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Laboratory Values				
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life- threatening consequences	pH < 7.3 with life-threatening consequences

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life- threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin*[13], *High* *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High *Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15] Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

21.2 Appendix 2: Summary of Protocol Amendments

The Summary of Protocol Amendments is provided as a separate document and maintained in the Trial Master File.

22 ATTACHMENTS

22.1 Attachment: Country-specific Information

ATTACHMENT: COUNTRY-SPECIFIC INFORMATION CLINICAL STUDY PROTOCOL MDGH-MOX-3002 DRC - VERSION 02, 30 JUNE 2020

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Table 1: Abbreviations and Acronyms

Abbreviation	Term
CECA/20	20e Communauté Evangélique au Centre de l'Afrique
CRMT	Centre de Recherche en Maladies Tropicales
DPS	Division Provinciale de Santé
DRC	Democratic Republic of Congo
EDCTP	European & Developing Countries Clinical Trials Partnership
GCP	Good clinical practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PICF	participant information and informed consent and assent forms
USH	Ugandan Shilling
ZSR	Zone de Santé Rurale

2 Introduction

In the Democratic Republic of the Congo (DRC), the study will be conducted in Ituri Province and may be conducted in an additional area to be identified.

3 Ituri Province

3.1 Investigator Organization

The study will be coordinated by the research team at the Centre de Recherche en Maladies Tropicales (CRMT).

CRMT was one of the research centers established for the moxidectin Phase III study (protocol ONCBL60801). It is located at the Referral Hospital (Hôpital de Réference) in Rethy, Ituri Province, and managed by the 20th Communauté Evangélique au Centre de l'Afrique (CECA20), Bunia, member of the Église du Christ au Congo, in DRC.

3.2 Study Team

The study will be led by Dr. T. Ukety, who is an ophthalmologist from Ituri, has conducted onchocerciasis-related studies in northeastern DRC (Ituri) prior to joining WHO and was involved in the Phase III study as a technical advisor.

The co-investigator, Dr. M. Mandro, is also from Ituri, has conducted onchocerciasis-related studies in Ituri and was a clinical monitor of the moxidectin Phase III study, in particular the site in Ituri. He has been seconded to this study from the DPS Ituri.

Some staff who conducted the Phase III study in Ituri will be involved in this study as well.

These staff, as well as additional staff hired for this study, will undergo (re)training on the ethical requirements for study conduct, the requirements for study conduct as outlined in the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP), the protocol, protocol required procedures and protocol required documentation.

The Standard Operating Procedures established for the Phase III study will be adapted or complemented for the study procedures required in this study.

3.3 Site Capacity

Establishment of the CRMT in preparation for the Phase III study included renovation of buildings not used by the Hôpital de Réference to provide rooms and facilities required for that study. These facilities, including laboratories, locked storage facilities for study documentation, locked and temperature controlled room for the storage and preparation of investigational product, a meeting room and staff offices will be used for this study.

Clinical, ophthalmological and laboratory equipment and material and other infrastructure elements such as cars, motorcycles, back-up generators, fuel reservoirs and communication means (satellite dish for internet connectivity) were also provided for the Phase III study and will be utilized for this study as needed. Additional and/or replacement equipment and material needed for this study will be purchased by CECA20 from the grant obtained from the European and Developing Countries Clinical Trials Partnership (EDCTP) by the Sponsor, the Investigator (Dr. T. Ukety, CECA20) and Co-Investigator (Dr. M. Mandro, DPS Ituri) and other co-applicants.

3.4 Recruitment areas

In Ituri (Figure 1) the study will be conducted principally in the Zone de Santé Rurale (ZSR) Logo, with possible extension of the recruitment area into the ZSR of Nyarambe (primary recruitment area) (Figure 2).

In view of civil unrest in these areas or the Ebola outbreak possibly preventing implementation or completion of the study in that area, the ZSR of Aru is planned as the backup recruitment area (Figure 3).

Figure 1: Map of the Democratic Republic of Congo with its 26 Provinces

Figure 2: Map of the Zone de Santé Rurale (ZSR) Logo with adjacent ZSR Nyarambe in Ituri Province (primary recruitment area)

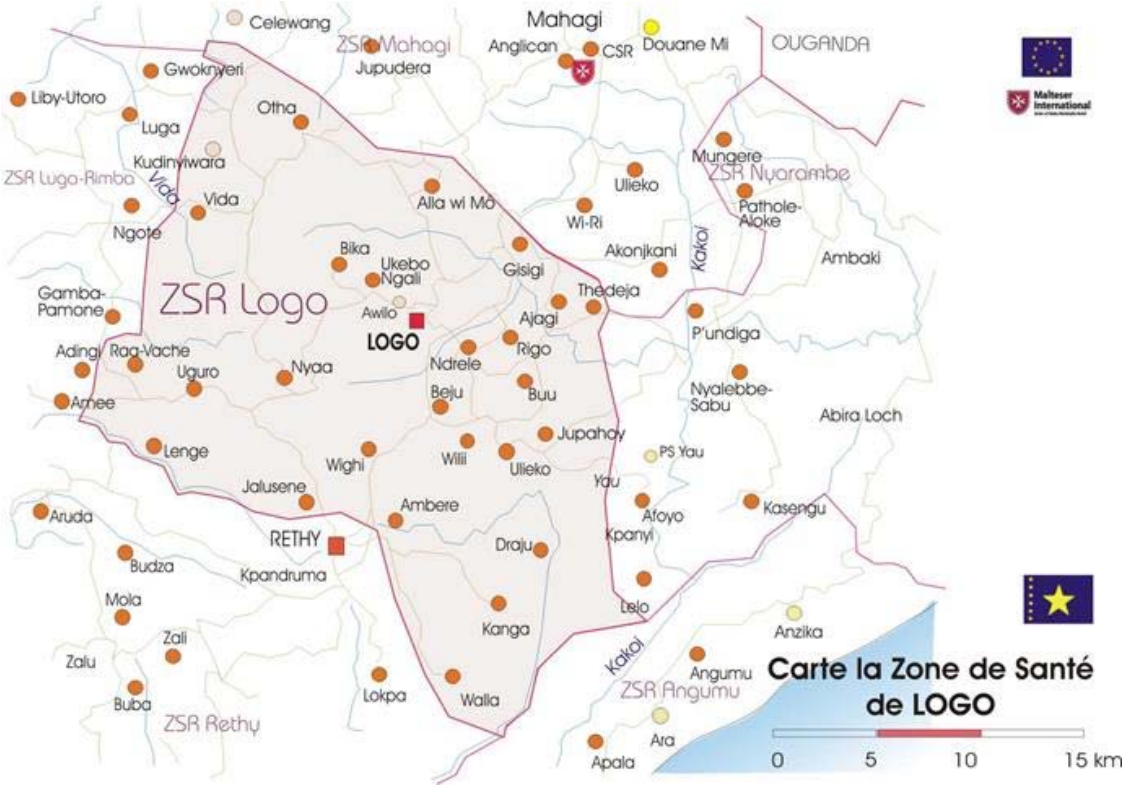
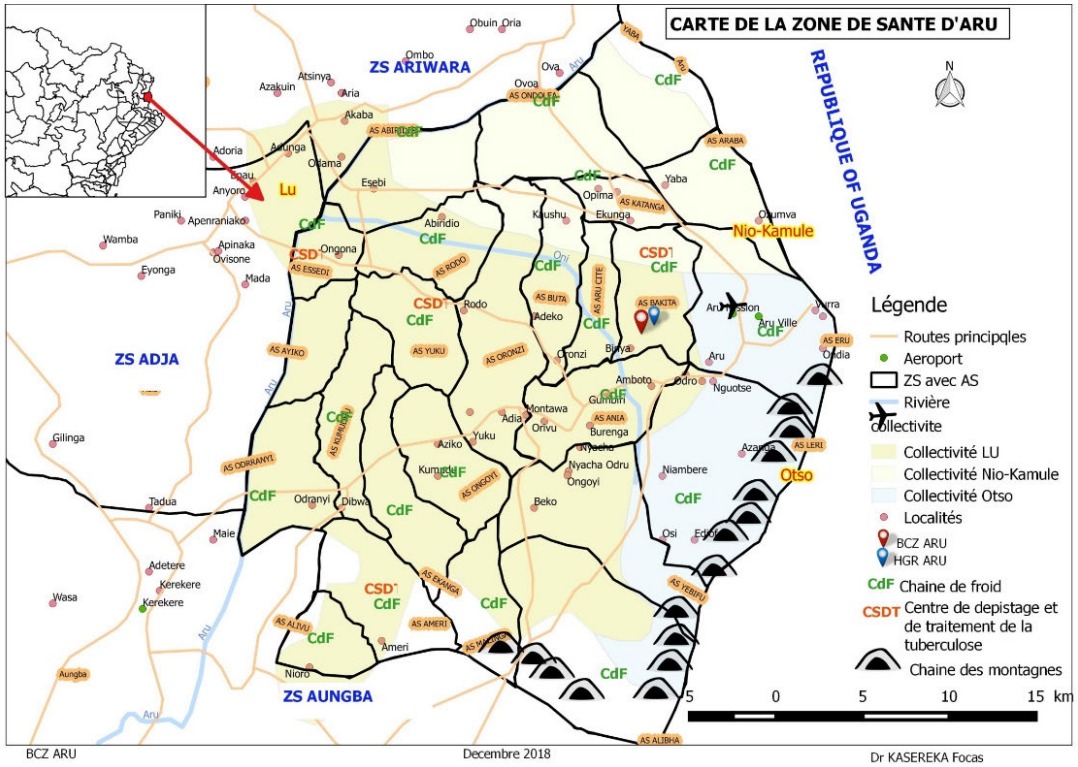


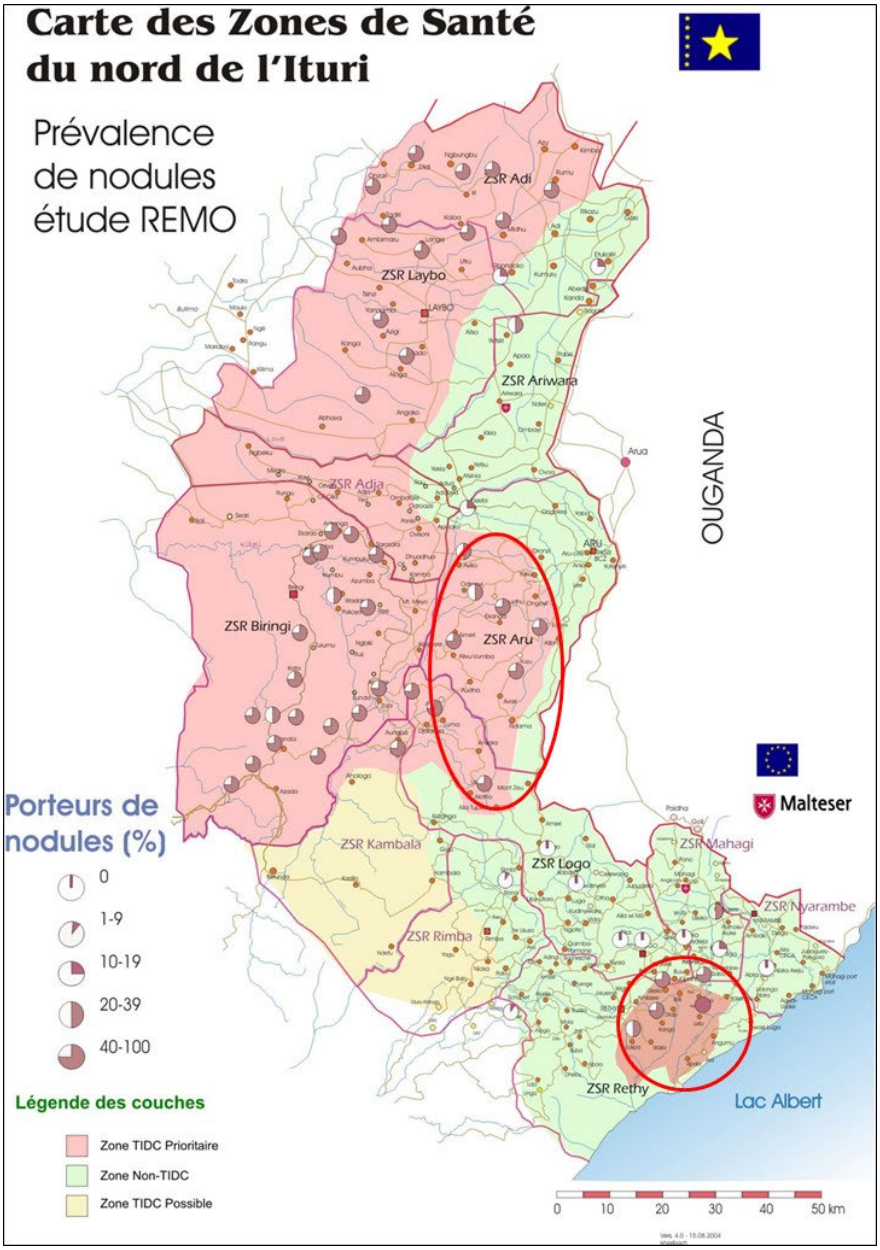
Figure 3: Map of the Zone de Santé Rurale (ZSR) Aru in Ituri Province (backup recruitment area)



The primary as well as the backup recruitment areas were selected for the following reasons:

- Epidemiological surveys conducted by the national onchocerciasis control program in 2002 indicate that many villages are onchocerciasis meso- or hyper-endemic (Figure 4) and
- Data obtained during screening in the ZSR Logo for the Phase III moxidectin study found 66.7% were infected with *O. volvulus* (by skin snip); and
- The areas are not endemic for *Loa loa* infection.
- Ivermectin mass drug administration has not yet been implemented (ZSR Logo and Aru) or only relatively recently (since 2016 in the ZSR Nyarambe for lymphatic filariasis control).

Figure 4: Results of Rapid Epidemiological Mapping (REMO) of onchocerciasis conducted by the national onchocerciasis control program Ituri Nord in 2002 with the primary and backup recruitment areas encircled in red



Considerations for identifying the villages from which individuals will be recruited will include the following:

- Acceptability of the research to the village community;
- Prior information on onchocerciasis endemicity including, but not limited to, available endemicity data and/or proximity to known vector breeding sites;
- The number and timing of prior ivermectin treatment rounds;
- Accessibility of the village;
- Vicinity of the village to local health centers.

3.5 Cultural and Socio-economic Characteristics of the Population from which Participants will be Recruited

3.5.1 Primary Recruitment Area

In the rural areas of the ZSR of Logo and in the villages in the ZSR Nyarambe, 98% of population are from the Alur ethnic group. In the Aire de Santé targeted for recruitment, 100% of the population speak the Alur language (Dhu-Alur). The other languages spoken are Lingala (20% of the population) and French (60% of the literate population) and Kiswahili (5%).

Consequently, the information documents and the discussion about the studies will be in Dhu-Alur. The Principal Investigator is Alur.

The most practiced religion across the primary recruitment area is Catholicism (80%). There is a growing presence of traditional religions such as “Mungu lonycon” or “Karwo” who believe that God is all powerful and able to solve all problems in response to prayers and whose leaders are preaching against modern health care. Special advocacy work with these leaders is required to encourage participation in health programs, as well as to obtain their permission to approach the communities regarding research studies.

The belief in the effectiveness of traditional healers is also high.

The majority of the population is poor and lives off agricultural activities, including subsistence farming. The area is known for production of coffee, mostly sold in Uganda, which constitutes the main source of income and employment in this region.

The area is characterized by high fertility rates, poor nutrition and low educational attainment with high rates of illiteracy. Less than 20% of the girls come to complete the secondary school.

Children have a very high degree of respect for their parents and the elderly. Children and adolescents usually live with their parents until they get married. Orphans live with other family members. The head of the household is their ‘guardian’ and makes all decisions for these minors without there necessarily being an ‘official document’ attesting this. Minors may also be sent by their parents to live with other relatives.

The average daily earning is around 5 US Dollars. The currency most frequently used is the Ugandan Shilling (USH).

3.5.2 Backup Recruitment Area

The majority of the population in the ZSR Aru are from the Lugbara ethnic group (around 90%) and speak Lugbara-tii (75%) and Lingala (25%). However, Lingala speakers live in the urban areas, not the rural areas where recruitment would take place.

Consequently, to prepare for conduct of the study exclusively or partly in the rural areas of the ZSR Aru, the information documents have been translated into Lugbara-tii ~~and into Lingala~~ and the discussions about the studies will be in Lugbara-tii.

The most practiced religions are Catholicism (40%) and Protestantism (35%) with other religions practiced by around 25% of the population. Aru territory is, like Logo, characterized by high levels of fetishism practice and belief in traditional healers.

The other cultural and socioeconomic characteristics are similar to the ones described for the primary recruitment area.

3.6 Concurrent recruitment into Study MDGH-MOX-3002 with recruitment into Study MDGH-MOX-3001

During the initial period of recruitment into study 3002, recruitment will be conducted concurrently with recruitment into study 3001. Details are provided in the protocol for study 3001 (submitted concurrently with the protocol for study 3002).

Briefly, volunteers not qualifying for study 3001 or deciding that they do not want to participate in study 3001 once they have been informed about the results of screening but who qualify for study 3002, will be provided the option to participate in study 3002.

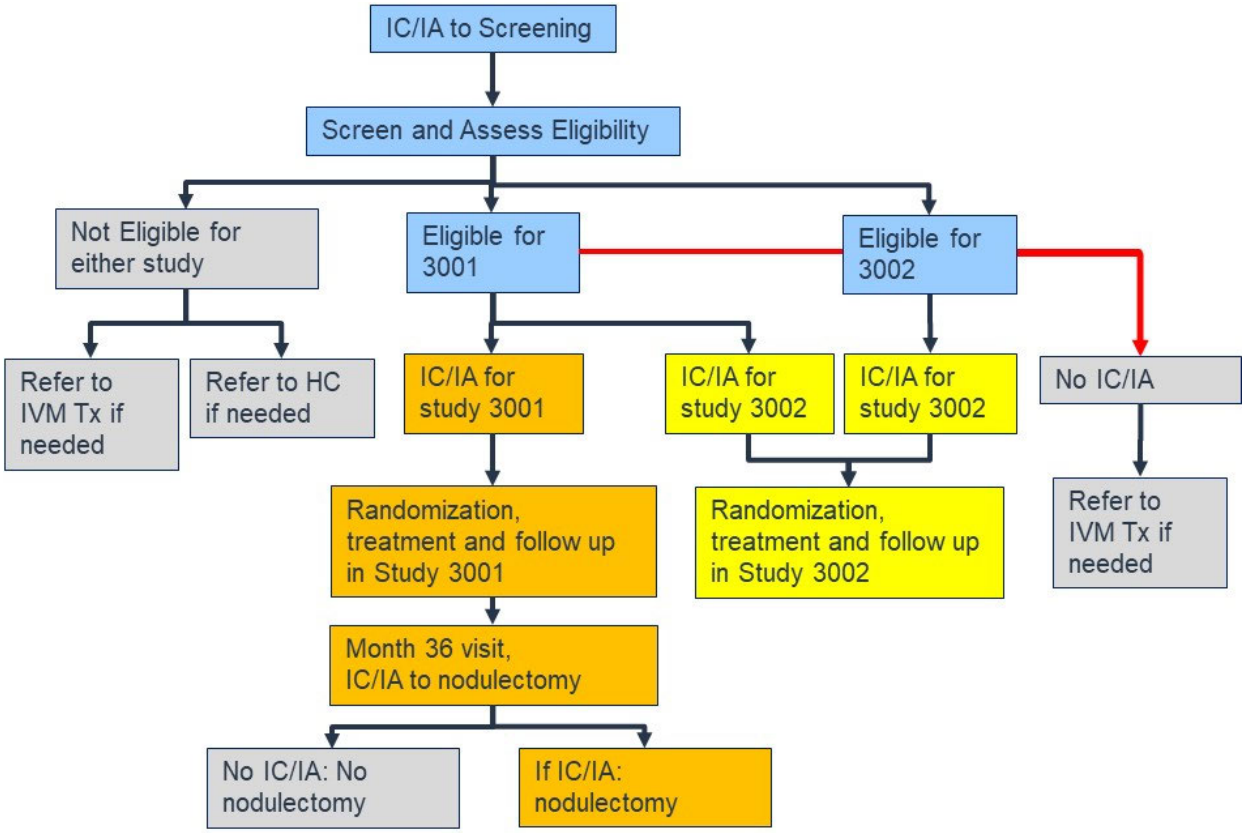
Concurrent conduct and recruitment into both this study and Study 3001 was decided upon to avoid having to tell people not eligible for study 3001 or not wanting to commit to study 3001 which lasts 3 years, but interested in participating in a study to come back later when individuals with their characteristics and interests 'are wanted'. Such an approach is considered disrespectful of their interests and their time, since they would have to be screened again and may at that time not be eligible for study 3002 anymore.

During concurrent recruitment informed consent/assent is divided into informed consent/assent for Screening for eligibility and informed consent/assent for participation in the study the participant is eligible for or chooses. Figure 5 provides an overview. For further information see Section 6 of the protocol for study 3001.

Provisions for Informed Consent/Assent to Study 3002 following completion of the period of concurrent recruitment are provided in the Main Protocol for study 3002.

The same principles for obtaining Informed Consent/Assent will be followed during both periods of recruitment (see Section 15.9 in both protocols)

Figure 5: Overview of Stepwise Informed Consent/Assent



Legend: C/IA = Informed Consent/Assent, Tx = Treatment, HC = Health Center, IVM = ivermectin

3.7 Compensation for Study Participants

As study participants will be recruited among villagers who are continuing to pursue their usual daily activities, the time participants spend on study activities will be time they are unable to pursue gainful work. To compensate study participants for the resulting loss of earnings, participants will be compensated for the time spent undergoing assessments based on the average daily earning of the population from which the study participants are being recruited, estimated by the Investigator at 5 US Dollars (US$). This is the equivalent of approximately 8500 Congolese francs (CDF) and approximately 20 000 USH, the currency commonly used in both the primary and back-up recruitment areas. The exchange rates vary over time and the local population is very familiar with the impact of these variations. To minimize participants suffering financially from exchange rates becoming unfavorable to them, the compensation is set based on the US$ and will be provided at the up-to-date exchange rate and in the currency the individual participant choses.

3.8 Considerations During the Development of the Participant Information Documents

In addition to the considerations during the Development of the Participant Information Documents (PICF) provided in Section 15.9.1 in the main protocol, the PICF were written to fit the notions in the population in the recruitment areas to ensure that they are familiar with specific concepts (e.g. currency exchange rates) or that unfamiliar concepts are explained (e.g.

blinding) or presented in terms meaningful to the potential participants (e.g. randomization as 'decided by chance', insurance as 'Sponsor having put money aside', password-protected as 'in a locked and secure area').

3.9 Preservation of Urine Left-over from Pregnancy Tests and Use for Improved Tools and Strategies for Control/Elimination of Onchocerciasis and other Neglected Tropical Diseases

Urine is a valuable resource for research into biomarkers as well as new drugs and vaccines. Therefore, CECA/20, the Sponsor and FR3, the repository that will receive the parasites obtained in this study (see Main Protocol Section 15.20.1), have agreed that urine samples left over from the pregnancy tests (see Main Protocol Section 7.4.5) should be provided to FR3. The extent to which this will be possible will depend on the funding that FR3 can raise for a freezer for short term storage at CRMT, provision of barcode-labeled storage vials, shipment on dry ice from DRC to FR3 and freezer space available at FR3.

The following special provisions are being put in place for minors.

After minors who have agreed to participate in the study become adults, they will be asked whether they continue to agree to study participation (see Main Protocol Section 15.9.3) and, if applicable, to the use of the left-over urine for future research. In case they change their mind, the Material Transfer Agreement between the Sponsor and CECA/20 and FR3 includes the following provisions:

- Samples identified as coming from minors will be put 'in quarantine' at FR3, i.e. will not be shipped to any requesters. They will be moved out of quarantine only after confirmation from the Sponsor or CECA/20 that the minor has confirmed agreement to future use of the left-over samples upon becoming an adult.
- Upon receipt of information from the Sponsor or CECA/20 that the minor has not maintained agreement to future use of left-over samples when becoming an adult or that further follow up of the minor for consent to future use of the left over samples is not possible, FR3 will retrieve and destroy the samples.

Retrieval of samples for 'moving them out of quarantine' or for destruction is made possible through the bar code system based sample management in place at FR3 and the fact that FR3 will provide bar-code labelled vials to CECA/20 for shipment of the samples.

For provisions for specimen anonymity and Material Transfer Agreement see Main Protocol Section 15.19.

3.10 DEC-Patch Evaluation, Shipment, Dispensation and Accountability

The DEC-Patch will not be evaluated during screening for concurrent recruitment into Study MDGH-MOX-3002 and Study MDGH-MOX-3001 (see Section 3.6). Furthermore, beginning of evaluation of the DEC-Patch will depend on availability of all required documentation and thus arrival of the DEC-Patch at CRMT.

DEC-Patches will be shipped to the site from Germany only after

- the letter on DEC-Patch provision to be sent by WHO to the Ministry of Health has been returned to WHO signed by the Ministry of Health,
- relevant export and import permits into DRC have been obtained and

- the Sponsor has confirmed that all relevant authorizations and Sponsor documentation requirements for the study and DEC-Patch evaluation have been met.

Shipment to the site may occur before the Site Initiation Visit with secure storage at the site under quarantine, until the study has been initiated. DEC-Patches will be stored and transported at ≤25 ºC. For transport between the CRMT and the villages, CRMT will have been provided with cold storage boxes.

Evaluation of the DEC-Patch during screening does not require blinding. Consequently, the DEC-Patch can be dispensed (envelope opened) as well as administered by blinded study team members. Dispensation and administration will be recorded by these study team members in source documents.

The Investigator will be responsible for ensuring accurate records are maintained for all DEC-Patches received, dispensed, dispensed and not administered, administered, returned or destroyed. The inventory, dispensing and administration logs must be available for inspection by the ~~un~~blinded Study Monitor or the unblinded Study Monitor.

DEC-Patch supplies must be accounted for by the blinded Study Monitor or the unblinded Study Monitor, and DEC-Patches not dispensed returned to the Sponsor for destruction at the end of the study or provided to the Ministry of Health if the Ministry of Health requests it. Copies of the records of DEC-Patches returned to the Sponsor must be retained by the Investigator.

As required by national law and in consultation with the sponsor and the Ministry of Health, unused DEC-Patches may be destroyed locally consistent with the local regulations. Copies of records on the destroyed DEC-Patches shall be retained by the Investigator. These records must show the quantity of DEC-Patches disposed of, the method of destruction, and the person who disposed of the DEC-Patches. Copies of such records shall be submitted to the Sponsor.

3.11 Overview of Measures to Minimize Risk of Transmission of SARS-CoV-2 virus during study conduct based on national/local guidance as of 30 June 2020

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Across all	Across all		• All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & Maladie de Virus Ebola (MVE)" • All communication about and community engagement regarding COVID-19 (Communication des risques et engagement communautaire en réponse à la COVID-19) will occur in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & MVE" and use their communication material.
Community mobilization (Sections **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**)	Government authorities; Provincial and national parliament members; Provincial and Territory and Health Zone authorities and staff	Yes	• By the time community mobilization is initiated, all members of this 'target population' will have already undergone education on COVID-19, and procedures for screening for COVID-19 symptoms before entering their buildings will have been put in place and everybody will wear masks. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • The offices/meeting rooms of the 'target population' will have already been set up for physical distancing and procedures will have been put in place to refer anybody with COVID-19 symptoms to the designated local health facility/COVID-19 team. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	'Target Population'	Physical Distancing possible	Information on physical distancing or measures to be taken to reduce risk of transmission
	Civil society (e.g. associations of different professional, religious groups, non-governmental organizations), Local staff of Local media staff	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • Study team will bring thermometers for temperature measurements and inform, as necessary, participants about COVID-19 related requirements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health /COVID-19 team. They will be excluded from the meeting. • Study team will ensure that all passing this screening will wash hands before entering the room and wear masks throughout the meeting. • Study team will ensure meeting space is set up to allow physical distancing. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Community mobilization (Sections **Error! Reference source not found.**, **Error! Reference source not found.**)	Religious Leaders, Village/ Community Leaders, Elders, Relais Communautaires (RECOs)	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged per village, and include not more than 20 participants, including not more than 10 chiefs and elders (typically 5), 5-7 RECOs and approximately 3 study team members. • Meetings will be set up in open spaces, a church or a school with study team ensuring seating is arranged for physical distancing. • Study team will bring thermometers for temperature measurements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health facility (or the study team will call the health facility/COVID-19 team on their behalf). They will be excluded from the meeting. • Study team will be bringing megaphones and cloth masks for all meeting participants, and ensure availability of soap and water (or hand sanitizers) for handwashing at the beginning and the end of the meeting. • Study team will ensure that all meeting participants wash hands before entering the meeting space, wear masks all along the meeting and wash hands at the end of the meeting. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents and cloth masks distributed will be left with meeting participants who will be advised to bring the mask to subsequent meetings.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Consultation with village communities and providing information required for village members to decide on participation in the study (Section **Error! Reference source not found.**)	Village inhabitants	Yes	• By the time community mobilization is initiated, the communities will have undergone education on COVID-19. • While the pandemic is ongoing, the community meetings as per protocol section **Error! Reference source not found.** will be preceded by a meeting with heads of families to provide them with a short overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing, demonstration on proper use and cleaning of cloth masks and the arrangements for further meetings with their family members about the study. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • The 1st and 2nd meeting as per Section **Error! Reference source not found.** will be arranged to take place with no more than 20 meeting participants including 1 RECO, 1 potential (or selected) literate witness, and up to 16 members of 3-4 families (and two or three study team members). • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs.
Provision of informed consent / assent (Sections **Error! Reference source not found.**, **Error! Reference source not found.**)	Village inhabitants interested in study participation	Yes	• Meetings between 1 study team member (or 1 study team member plus 1 translator) and an individual wanting to provide informed consent (or a minor with their parent(s)/guardian wanting to provide informed assent and consent) and the literate witness will take place in a setting that will allow physical distancing. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • All will be asked to bring the cloth masks provided to them to the next meeting (study visits).

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
All study visits (Section **Error! Reference source not found.**)	Screening/study participants	Yes/No	• All study team members will wear masks and gloves during all interactions with study participants. • (Potential) participants will be asked to bring and wear the cloth masks they were provided with during the meetings in which they were informed about the study. • Soap and water (or hand sanitizers) will be brought so that each visit can be initiated and end with hand washing/sanitizing. • Staff members will wash/sanitize hands and change gloves between interactions with different participants. • Areas where screening/study participants can wait will be set up with physical distancing. • At the beginning of each study visit a study team member will measure the temperature of all participants and ask them about COVID-19 symptoms, will advise them to self-isolate and either ask them to call the designated health facility/COVID-19 team or call that health facility/COVID-19 team on their behalf. If they are identified by the health facility/COVID-19 team as not COVID-19 infected, the relevant study visit will be rescheduled. If they are identified as COVID-19 infected, study visits will be arranged to take place after they have been confirmed as recovered by the designated public health staff. • All equipment will be sanitized between use on different participants.